Eur Respir J, 1996, 9, 1306–1313
DOI: 10.1183/09031936.96.09061306
Printed in UK - all rights reserved

European Respiratory Journal
ISSN 0903 - 1936

TECHNICAL NOTE

Improvement of tidal breathing pattern analysis in children with asthma by on-line automatic data processing

C.K. van der Ent*, H.J.L. Brackel*, P. Mulder**, J.M. Bogaard+

Improvement of tidal breathing pattern analysis in children with asthma by on-line automatic data processing. C.K. van der Ent, H.J.L. Brackel, P. Mulder, J.M. Bogaard. ©ERS Journals Ltd 1996.

ABSTRACT: The time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time (t_{PTEF}/t_E) during tidal breathing (TB) is used as a parameter of airway obstruction in children with asthma. Curve selection bias is one of the most important limitations to the method. This study evaluates three curve selection methods, including a computer program, which on-line selects and analyses TB curves (Masterscreen Paediatric; Jaeger, Germany).

TB analysis was performed in 26 children (aged 4–7 yrs) with asthma, before and after methacholine provocation and after subsequent bronchodilatation. Levels and stability of TB parameters derived from computer-selected, unselected and unbiased eye-selected curves were compared.

t_{PTEF}/t_E ratios of the computer-selected curves agreed well with the unbiased eye-selected curves (limits of agreement -4.8 and +5.8%), but were significantly different from the ratios of unselected curves. Computer-derived t_{PTEF}/t_E ratios had the highest level of stability: the reliability coefficient of baseline measurements was 0.96 for computer selection, 0.84 for eye selection and 0.87 for no selection (reliability index = 1 at maximal stability). Tidal volume, respiratory rate, inspiratory and expiratory time were also assessed accurately by the computer program. The mean t_{PTEF}/t_E ratio (computer selection) dropped after methacholine provocation (from 30±9 to 22±9% at provocative dose at which forced expiratory volume in one second had dropped ≥20% from baseline (FEV1-PD20 level), $p<0.001$) and was restored after bronchodilatation (30±6%; $p<0.001$).

We conclude that on-line computer analysis is preferable to no selection and to by-eye selection. The use of the program avoids curve selection bias and enhances the applicability of tidal breathing analysis as a measure of airflow obstruction in young children.

Eur Respir J., 1996, 9, 1306–1313.

*Wilhelmina Children's Hospital, University Hospital for Children and Youth, Dept of Paediatric Pulmonology, Utrecht, The Netherlands. **Erasmus University, Dept of Epidemiology and Biostatistics, Rotterdam, The Netherlands. +University Hospital Dijkzigt, Pathophysiological Laboratory, Dept of Pulmonary Diseases, Rotterdam, The Netherlands.

Correspondence: C.K. van der Ent
Wilhelmina Children's Hospital
University Hospital for Children and Youth
Dept of Paediatric Pulmonology
P.O. Box 18009
3501 CA Utrecht
The Netherlands

Keywords: Asthma
children
computer-analysis
selection
tidal breathing

Received: October 12 1995
Accepted after revision March 12 1996

This study was supported by a financial grant from Glaxo-Wellcome

In recent years, an increasing number of reports have appeared on the applicability of tidal breathing analysis as a measure of airway obstruction in infants and children [1]. MARTINEZ and co-workers [2, 3] showed that the time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time (t_{PTEF}/t_E) is predictive of subsequent wheezing in children during the first 3 yrs of life. From that time, the question of whether t_{PTEF}/t_E is a reliable measure of airway obstruction has frequently been discussed [4–14]. The question remains partially unresolved, because these studies have marked methodological differences. They describe t_{PTEF}/t_E in concordance with several other, more or less, reliable measures of airway obstruction. Different authors focus on infants, others on children of different ages. The value of t_{PTEF}/t_E probably changes with age, most clearly during the first 6 months of life. Curve selection in analysing tidal breathing patterns is one of the most important - if not the most important - causes of bias. Most authors use a curve selection by-eye; and also the number of breathing curves which is used to calculate t_{PTEF}/t_E varies widely.

To avoid selection bias in tidal breathing analysis, a computer program was developed which can easily select and evaluate large samples of tidal breathing curves (Masterscreen Paediatric; Jaeger, Germany). The present study was performed: 1) to evaluate the validity of this computerized method of on-line breathing curve selection and calculation of parameters; and 2) to evaluate the influence of airway obstruction on the calculation of tidal breathing parameters in awake young children with asthma.

Subjects

Methacholine provocation was performed in 26 children (aged 4–7 yrs) with mild to severe asthma according to the international consensus report on diagnosis and treatment of asthma [15]. All children were treated with inhaled steroids (beclomethasone or budesonide 200–800 μg·day^{-1}) and rescue medication (salbutamol or terbutaline). They were all free of complaints during the period of the study and were not allowed to use

Table 1. – Demographic data and baseline pulmonary function data of 26 children with asthma

Age yrs	6.5±0.9
Height cm	120±7
Body weight kg	23±4
Sex M/F	19/7
FEV_1 mL	1480±270
FEV_1 % pred	107±11

Values are presented as mean±SD. M: male; F: female; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value.

bronchodilators during 24 h prior to the test. All children had increased immunoglobulin E (IgE) levels and *Dermatophagoides pteronyssinus* specific IgE antibodies in serum. Children who were not able to perform maximal expiratory flow volume measurement or who had a forced expiratory volume in one second (FEV_1) of less than 75% of predicted were excluded from participation in the study. Patient characteristics are summarized in table 1.

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

Methods

Maximal expiratory flow volume (MEFV) measurements

MEFV measurement was performed in all children, with use of a pneumotachometer system (MasterScreen Pneumo; Jaeger, Germany). The best MEFV curve, according to the American Thoracic Society (ATS) criteria, from at least five trials was used [16]. Data were stored and processed in a 486 sx Notebook computer. All values were corrected to body temperature, ambient pressure and saturation with water vapour (BTPS) conditions. For reference values, data of ZAPLETAL *et al.* were used [17].

Methacholine provocation

Methacholine provocation was performed according to a standardized protocol [18]. Methacholine aerosols were generated by calibrated DeVilbiss 646 nebulizers with closed vents and 3 mL methacholine bromide solution in buffered saline in the vial. The nebulizer was attached to a Rosenthal dosimeter. During a deep inspiration with sufficient airflow, the dosimeter was triggered for 0.6 s. A total of 20 µL of aerosolized solution was delivered in four consecutive breaths *via* a mouth tube. After performing baseline MEFV measurement, saline was inhaled to rule out nonspecific reactions and, subsequently, methacholine was administered in doubling doses. Methacholine mouth doses of 3, 6, 12, 24, 50, 98, 196, 392 and 784 µg were administered. MEFV measurement was performed 3 min after every dose of methacholine. Provocation was continued until the dose at which FEV_1 had dropped 20% or more from baseline (PD_{20}). After this dose, 200–400 µg of salbutamol dose-aerosol was administered *via* a Volumatic®. After 15 min lung function tests were repeated.

Tidal breathing analysis

Tidal breathing analysis was performed three times in all children: before methacholine challenge; during airway obstruction, *i.e.* immediately after reaching PD_{20}; and after subsequent bronchodilatation. Tidal breathing analysis was performed with the Masterscreen Paediatric system (Jaeger).

Procedure. During tidal breathing analysis, the children were sitting upright in an easy chair, with their head resting against the back of the chair. They were instructed to breathe normally in a well-fitting silicone face mask.

Tidal breathing airflow was recorded by a Lilly pneumotachometer with a flow range of 0–20 $L \cdot s^{-1}$. The total resistance of the flow sensor was below 50 $Pa \cdot L^{-1} \cdot s$, and the dead space of the pneumotachometer was 90 mL. The pressure drop was measured by a differential pressure transducer (pressure range of ±1 kPa).

Computer analysis. After BTPS correction, the flow was digitally integrated to volume at a rate of 500 Hz. The sampling rate of the tidal breathing analysis program for flow and volume can be set to match the different needs for different patient groups. For fast-breathing babies, a maximum sampling rate of 250 Hz is possible. In slower-breathing children, sampling rates of 166 or 100 Hz can be selected. The sampling rate selected influences the resolution of the times and volumes determined as well as the resolution of the ratios calculated. In this study, the 100 Hz sampling rate was selected, which leads to a resolution of 10 ms in time determination and a typical resolution of 2% (assuming time to peak flow of 500 ms). By averaging several breathing cycles, the inaccuracy caused by this resolution improves.

Peak tidal expiratory flow was determined by searching for the sample with the highest flow value in each breathing cycle. The onset of expiration was defined as the last change of airflow direction before the peak flow, and the end of expiration was defined as the next change in airflow direction after the peak flow.

For each consecutive breathing cycle, the time taken to achieve peak tidal expiratory flow as a proportion of total expiratory time (t_{PTEF}/t_E) and the volume taken to achieve peak tidal expiratory flow as a proportion of total expiratory volume (V_{PTEF}/V_E) were calculated on-line.

After each expiration, the last series of breathing cycles were evaluated statistically. Supposing that most breathing artifacts (*e.g.* swallowing, hiccups) are in the outer quartiles of the calculated t_{PTEF}/t_E and V_{PTEF}/V_E ratio ranges, the program automatically deleted the t_{PTEF}/t_E and V_{PTEF}/V_E values below the 25 percentile and above the 75 percentile for each parameter range. The mean and standard deviation of the remaining 50% interval around the median ratio was calculated. Breathing cycles with both ratios within the middle part were treated as representative. From these representative breathing cycles, mean inspiratory time (t_I), expiratory time (t_E), total breathing cycle time (t_{tot}), tidal volume (V_T), respiratory rate (RR) and minute volume (MV) were calculated.

The number of breathing cycles analysed can be selected in the program (minimally 6, maximally 50 cycles). In this study, a sample size of 20 breathing cycles was selected. Thus, the t_{PTEF}/t_E and V_{PTEF}/V_E ratios in this

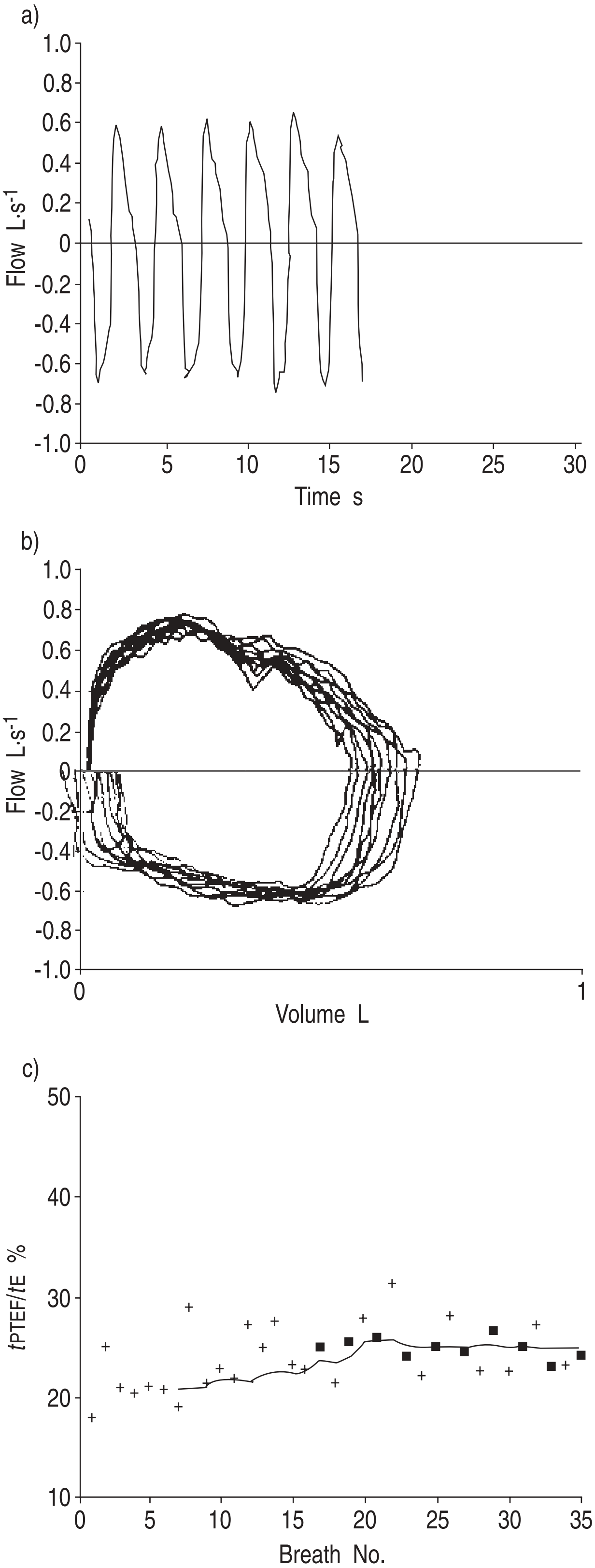

Fig. 1. – On-line computer display during tidal breathing analysis. a) On-line flow-time curve; b) On-line flow-volume display; c) trend-display, which shows the on-line calculated *t*PTEF/*t*E ratios. The blocks represent the ratios which are taken into the averaging. The on-line calculated mean value is indicated as a line (see text). *t*PTEF/*t*E: time taken to achieve peak tidal expiratory flow as proportion of total expiratory time.

study were the calculated means of the 10 middle values of the last 20 cycles of the recording.

To indicate the stability of the tidal breathing pattern, the calculated *t*PTEF/*t*E and *V*PTEF/*V*E ratios and the calculated momentary mean values of these ratios are displayed in a breath-by-breath diagram (trend-analysis) (fig. 1c). Independent of the relatively large scatter of the individual *t*PTEF/*t*E and *V*PTEF/*V*E ratios, the mean trends usually show stable values after a short period of adaptation (generally 20–30 s). In this study, the recording was continued during 20–25 tidal breathing cycles after achievement of these stable mean trends.

After ending the recording, a mean flow-time and a mean flow-volume curve was calculated from the representative breathing cycles by performing a time-based averaging of the flow and volume signals (fig. 2). By this procedure, the influence of noise on the signal was decreased. Representative mean flow-time and flow-volume curves can be displayed on screen or on a printed report. In displaying the final result the mean value, the standard deviation and the minimum and maximum of the *t*PTEF/*t*E and *V*PTEF/*V*E ratios are shown in a box-plot (fig. 2c).

After completing the recording the results were stored in the database. In the result phase, it is possible to toggle the status of single measured *t*PTEF/*t*E values on the breath-by-breath result screen to remove them from or add them to the average value. This possibility was not used in the "computer selection method" in this study.

Selection protocols. In this study, breathing curves for mean parameter calculation were selected in three different ways. The first method was the "computer selection" of 10 curves from the last recorded 20 breathing curves, as described above. The second method was the "no selection" method: all of the last recorded 20 breathing curves were toggled as valid and mean tidal breathing parameters were calculated from these 20 curves. The third method was unbiased "selection by-eye". For this method all curves were toggled as invalid. From the last recorded 20 breathing curves, 10 curves were selected by-eye and toggled as valid by an independent investigator who was unaware of the "computer selection" and "no selection" results. Valid curves were selected according to a well-described selection protocol [12]. Selection criteria were: 1) no doubtful points of zero-flow (*e.g.* no breathholding during or between the inspiratory and expiratory phase); 2) no doubtful point of expiratory peak flow (no more than one peak); and 3) the curve is not obviously different from the regular tidal breathing pattern (*e.g.* no deep sighs). When more than 10 of the 20 curves were toggled as valid, mean calculations were based on the last 10 valid curves of the recording. The *t*PTEF/*t*E from the by-eye selection of the independent investigator was regarded as "gold standard" for *t*PTEF/*t*E level.

Statistical analysis

Data are reported as mean±standard deviation, unless otherwise indicated. For comparison of data, Student's paired t-test was used. Spearman rank correlation coefficients were used to evaluate correlations. Analysis

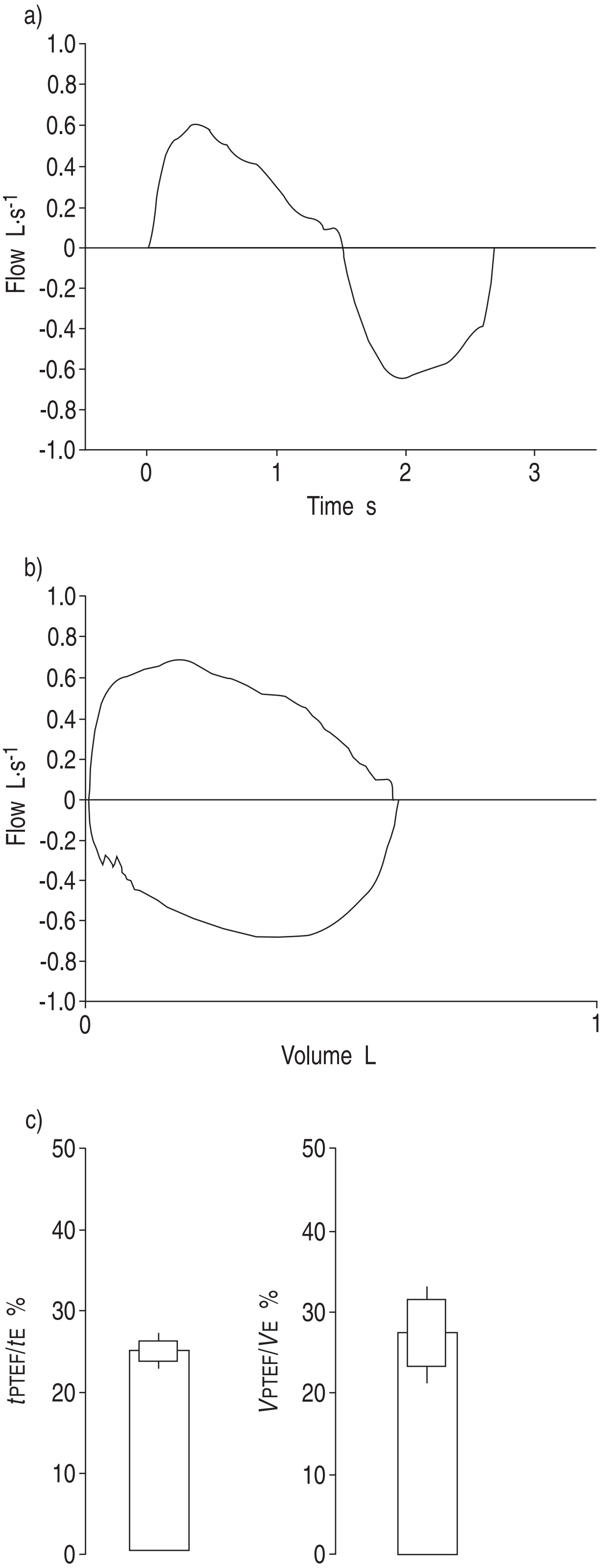

Fig. 2. – Computer screen during result phase of tidal breathing analysis (after ending the recording). a) Mean expiratory flow-time curve; b) mean flow-volume curve; c) box-plots representing mean values, standard deviations and range of $t_{\text{PTEF}}/t_{\text{E}}$ (left) and $V_{\text{PTEF}}/V_{\text{E}}$ (right) ratios, after standard computer selection. $t_{\text{PTEF}}/t_{\text{E}}$: time taken to achieve peak tidal expiratory flow as proportion total expiratory time; $V_{\text{PTEF}}/V_{\text{E}}$: volume taken to achieve peak tidal expiratory flow as proportion of total expiratory volume.

of agreement was performed as described by BLAND and ALTMAN [19]. For statistical evaluation of the stability of the $t_{\text{PTEF}}/t_{\text{E}}$ ratio, the reliability coefficient (RC) was used. A subjects true $t_{\text{PTEF}}/t_{\text{E}}$ ratio is estimated by taking the average over n breathing cycles within the subject. The RC of this average calculated $t_{\text{PTEF}}/t_{\text{E}}$ ratio is defined as:

$$\text{RC} = \frac{\sigma^2_{\text{inter}}}{\sigma^2_{\text{inter}} + \sigma^2_{\text{intra}}/n}$$

in which σ^2_{inter} is the between-subject variance of true $t_{\text{PTEF}}/t_{\text{E}}$ ratios, σ^2_{intra} is the within-subject variance of single $t_{\text{PTEF}}/t_{\text{E}}$ ratios within one subject, and n is the number of breathing cycles used to calculate the average $t_{\text{PTEF}}/t_{\text{E}}$ ratio within a subject. RC (also called intraclass correlation coefficient) reflects the within-subject stability of a calculated average $t_{\text{PTEF}}/t_{\text{E}}$ ratio (the nearer RC to 1, the more stable the average ratio).

Results

Computer selection versus *selection by-eye*

Mean $t_{\text{PTEF}}/t_{\text{E}}$ of all 78 measurements (three times in 26 children) using the computer selection was 26.5±8.7%. This was not significantly different from the mean $t_{\text{PTEF}}/t_{\text{E}}$ level when breathing curves were selected by-eye (26.0±8.2%; $p=0.12$). Mean values of the other tidal breathing parameters using the two different selection methods are summarized in table 2. There were no significant differences between computer and eye selection, except for a small difference in t_{E}.

The mean difference between the $t_{\text{PTEF}}/t_{\text{E}}$ ratio obtained by computer selection and selection by-eye was 0.5%. The standard deviation of the differences was 2.7%,

Table 2. – Tidal breathing parameters using three different curve selection methods

Method of selection	Computer	By-eye	No selection
$t_{\text{PTEF}}/t_{\text{E}}$ %	26.5±8.7	26.0±8.2	27.1±8.1
		(NS)	(p<0.001)
$V_{\text{PTEF}}/V_{\text{E}}$ %	28.4±7.9	28.0±7.5	28.9±7.2
		(NS)	(p<0.01)
V_{T} L	0.28±0.09	0.28±0.08	0.28±0.08
		(NS)	(NS)
RR breaths·min^{-1}	22.7±5.4	23.5±5.3	22.4±5.0
		(NS)	(p<0.001)
MV L	6.2±1.7	6.3±1.8	6.0±1.6
		(NS)	(p<0.001)
t_{I} s	1.23±0.31	1.19±0.28	1.22±0.28
		(NS)	(p<0.05)
t_{E} s	1.54±0.41	1.50±0.39	1.59±0.41
		(p<0.01)	(p<0.001)

Values are presented as mean±SD. Results were compared by paired t-test, and level of significance is presented in parenthesis. $t_{\text{PTEF}}/t_{\text{E}}$: time to achieve peak tidal expiratory flow as proportion of total expiratory time; $V_{\text{PTEF}}/V_{\text{E}}$: volume taken to achieve peak tidal expiratory flow as a proportion of total expiratory volume; V_{T}: tidal volume; RR: respiratory rate; MV: minute volume; t_{I}: inspiratory time; t_{E}: expiratory time; NS: nonsignificant.

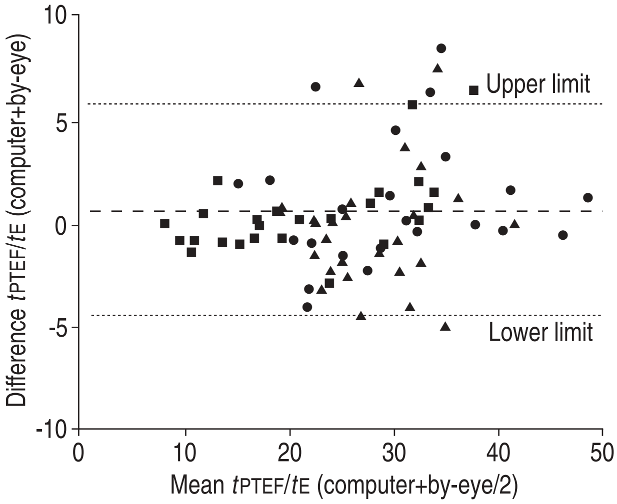

Fig. 3. – Analysis of agreement of mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratios calculated from computer selections and selections by-eye. ● : at baseline; ■ : after methacholine; ▲ : after salbutamol. For definitions see legend to figure 1.

indicating that 95% of the values of $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ obtained by computer selection fell between -4.8 and +5.8% of the eye-selected measurements ("lower and upper limits of agreement" as defined by BLAND and ALTMAN [19]) (fig. 3).

Table 3 shows limits of agreement for the other tidal breathing parameters.

Unselected curves versus *selection by-eye*

Mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ of all 78 measurements, when calculated from 20 unselected breathing curves was 27.1± 8.1%. This was significantly higher compared to the eye selection value ($p<0.001$; table 2). The mean values of $V_{\mathrm{PTEF}}/V_{\mathrm{E}}$, t_{I}, and t_{E} were also significantly higher compared to the eye selection values. RR and MV were significantly lower. No significant difference was found in V_{T} (table 2).

Ninety five percent of the no selection $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values were within -3.9 and +6.1% of the eye selection values. Limits of agreement between the eye and no selection parameters are summarized in table 3.

Computer selection versus *unselected curves*

Except for $V_{\mathrm{PTEF}}/V_{\mathrm{E}}$, RR and t_{I}, tidal breathing parameters derived from the computer selection method differed significantly from the nonselection method parameters. $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ and t_{E} were significantly lower in the computer selection ($p<0.05$ and $p<0.001$, respectively). V_{T} and MV were significantly higher compared to the no selection method ($p<0.05$ and $p<0.001$, respectively) (table 2).

Table 3. – Limits of agreement of tidal breathing parameters using three different selection methods

	Computer *versus* by-eye	No selection *versus* by-eye
$t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ %	-4.8 – +5.8	-3.9 – +6.1
$V_{\mathrm{PTEF}}/V_{\mathrm{E}}$ %	-5.6 – +6.0	-4.6 – +6.4
V_{T} L	-0.03 – +0.04	-0.03 – +0.03
RR breaths·min^{-1}	-5.4 – +4.6	-4.2 – +2.0
MV L	-1.34 – +1.25	-1.28 – +0.69
t_{I} s	-0.34 – +0.37	-0.20 – +0.26
t_{E} s	-0.16 – +0.20	-0.15 – +0.34

For definitions see legend to table 2.

Influence of airway obstruction

Mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ in 26 children using computer selection before methacholine provocation was 29.8±8.8%. After provocation at FEV$_1$-PD$_{20}$ level (mean FEV$_1$ 1,090±230 mL, 79±13% of predicted) $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ fell to 21.9±9.2% ($p<0.001$). In 21 children (81%) $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ decreased after methacholine, in five children (19%) $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ increased. After administration of salbutamol, lung function returned to normal values (FEV$_1$ 1,540±270 mL, 112±14% of predicted, not significantly different from baseline values). Mean computer selected $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ value was 27.9± 5.8%, which was not significantly different from baseline value. In 21 children (81%) $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ increased after salbutamol, in five children (19%) $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ decreased.

Mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values from selections by-eye equally fell after methacholine and were restored to baseline values after administration of salbutamol (table 4).

The fall and rise of the nonselected mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values after methacholine and subsequent salbutamol administration were significant, but p-values were lower compared to the changes in computer- and eye-selected measurements.

In all three different methods of breathing curve selection, V_{T}, RR, MV, t_{I} and t_{E} did not change significantly after methacholine or salbutamol administration.

Influence of the selection method on the stability of $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$

Using the no selection method, the calculated average $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratios of 20 breathing cycles correlated significantly with the standard deviation of these mean ratios with Spearman rank correlations of 0.64 (baseline), 0.65 (after methacholine) and 0.40 (after salbutamol). To

Table 4. – $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ at baseline, after methacholine provocation (FEV$_1$-PD$_{20}$) and after subsequent bronchodilation (salbutamol) using three different curve selection methods

	Baseline %	FEV$_1$-PD$_{20}$ %	Salbutamol %
Computer selection	29.8±8.8	21.9±9.2 ($p<0.001$)	27.9±5.8 ($p<0.001$)
Selection by eye	28.7±8.4	21.3±8.2 ($p<0.001$)	28.0±5.5 ($p<0.001$)
No selection	29.9±7.9	23.0±8.7 ($p<0.01$)	28.5±5.6 ($p<0.01$)

Values are presented as mean±SD. Results were compared by paired t-tests and level of significance is presented in parenthesis. PD$_{20}$: provocative dose of methacholine producing a ≥20% fall in forced expiratory volume in one second from baseline value. For further definitions see legends to tables 1 and 2.

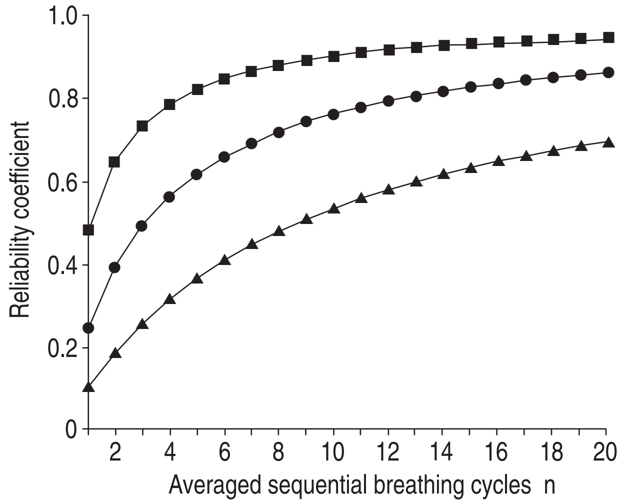

Fig. 4. – Reliability coefficients (RC) of the log ratio $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ at baseline (—●—), after methacholine (—■—) and after salbutamol (—▲—) when calculated as average of n sequential unselected breathing cycles. For definitions see legend to figure 1.

eliminate this correlation between level and variability, inter- and intrasubject variance ($\sigma^2_{\mathrm{inter}}$ and $\sigma^2_{\mathrm{intra}}$) were calculated on log transformed $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values.

In the no selection method, the $\sigma^2_{\mathrm{inter}}$ of log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ was estimated as 0.071 at baseline, 0.176 after methacholine and 0.029 after salbutamol; $\sigma^2_{\mathrm{intra}}$ was 0.218, 0.189 and 0.244, respectively. Consequently, the RC of a mean log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratio calculated from 20 unselected sequential breathing cycles was 0.87 at baseline, 0.95 after methacholine and 0.70 after salbutamol. RC can also be calculated when less than 20 sequential breathing cycles would be used to calculate an average log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ value. The use of one single breathing curve (n=1) results in a log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratio with RC of 0.25 at baseline, 0.48 after methacholine and 0.11 after salbutamol. Increase of the number of cycles will increase RC of the subsequently calculated mean log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratio (fig. 4).

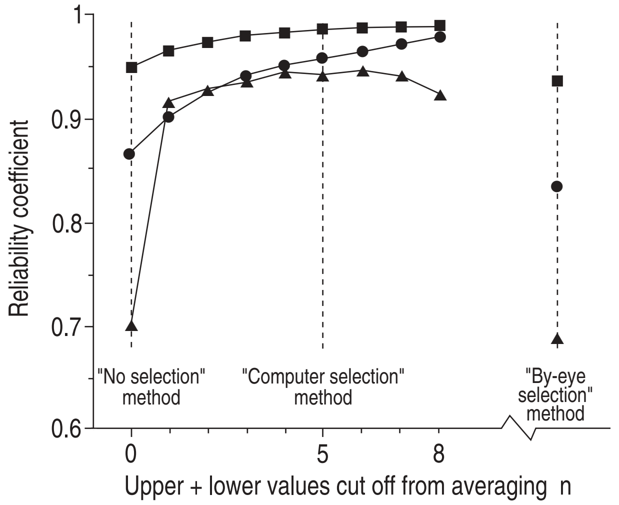

Fig. 5. – Reliability coefficients (RC) of the log ratio $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ when calculated as the average of 20 minus the n upper and n lower values. Reliability coefficients of the by-eye selection method are also indicated. ● : at baseline; ■ : after methacholine; ▲ : after salbutamol. For definitions see legend to figure 1.

In the by-eye selection method, $\sigma^2_{\mathrm{inter}}$ of log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ was 0.078 at baseline, 0.173 after methacholine and 0.030 after salbutamol; $\sigma^2_{\mathrm{intra}}$ was 0.151, 0.098 and 0.133, respectively. Consequently, RC of the mean log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratios of the by-eye selection in this study was 0.84 at baseline, 0.95 after methacholine, and 0.69 after salbutamol (fig. 5).

The computer selects breathing cycles by cutting off the five upper and five lower values of the parameter range of 20 breathing cycles. This process influences both $\sigma^2_{\mathrm{inter}}$ and $\sigma^2_{\mathrm{intra}}$ as well as n. The RC of the mean log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratios resulting from the standard computer selection was 0.96 at baseline, 0.98 after methacholine and 0.94 after salbutamol. Figure 5 displays the RC values of mean log $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratios, not only when 0 (no selection method) or 5 upper and lower values (standard computer selection) are cut off, but also when other numbers of outer values would be cut off.

Discussion

The present study addressed the question of whether the method of tidal breathing analysis can be improved by on-line automatic data processing. Three different methods of breathing curve selection were compared and the influence of airflow obstruction was studied. Several aspects of computer-based analysis are discussed.

Computer selection versus *selection by-eye*

This study showed a high level of agreement between $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values calculated from "regular" breathing curves selected by-eye by an unbiased investigator and those selected by the computer program. There were no significant differences between mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values of both selection methods and the limits of agreement were acceptably narrow. All other tidal breathing parameters showed comparable high levels of agreement between both methods of curve selection. In this study in unsedated young children with asthma, the computer program was equally as successful in selection of valid breathing curves for parameter calculation as the unbiased by-eye selection method in deleting "irregular" breathing cycles. Analysis of the stability (as reflected by the RC) of the resulting mean $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ values of both methods revealed a higher stability of the computer-selected ratios compared to the by-eye-selected ratios (fig. 5). The avoidance of selection bias in the clinical setting and the high level of stability of the $t_{\mathrm{PTEF}}/t_{\mathrm{E}}$ ratio made the computer selection method preferable to the by-eye selection method.

Unselected curves versus *selection by-eye*

All tidal breathing parameters showed the same levels of agreement between no selection and eye selection as between computer selection and eye selection (table 3). However, mean values of all tidal breathing parameters (except for V_{T}) from the no selection method were significantly different from the values of the unbiased eye selection values (table 2). The reliability coefficients of the tPTEF/tE ratios derived from the no selection method and the by-eye selection method were comparable, indicating a comparable level of stability. However, the systematic differences in tPTEF/tE levels between these two methods and the lower stability of the ratios compared to the computer selected ratios make the computer selection method more attractive.

All tidal breathing parameters (except for VPTEF/VE, RR and tI) of the no selection method were significantly different from the computer selection method.

tPTEF/tE as a parameter of airflow obstruction

tPTEF/tE was a parameter of airflow obstruction in this study. The mean value of the ratio significantly decreased during methacholine-induced airflow obstruction and returned to baseline after administration of salbutamol. This pattern was in line with other studies in young children. CUTRERA *et al.* [6] showed that tPTEF/tE was lower in school-age children with asthma compared to normals. CARLSEN and LODRUP-CARLSEN [14] and VAN DER ENT *et al.* [12] showed a rise of tPTEF/tE in children with asthma after administration of salbutamol.

In this study, 5 of 26 children showed an "adverse" change of tPTEF/tE after bronchoprovocation, and an equal number showed an increase of tPTEF/tE after bronchodilatation, This is in line with other studies [12, 14], and stresses that tPTEF/tE is more useful as a parameter of airflow obstruction in epidemiological research than in individual patients.

This study showed that unbiased selection by-eye and computer selection confirmed the fall and rise of tPTEF/tE levels during methacholine provocation and subsequent administration of salbutamol with equal levels of significancy (table 4). The differences in tPTEF/tE of the nonselection method had lower levels of significance. This was another reason to prefer the computer selection method above nonselection.

VT, MV, RR, tI, and tE did not change during airway obstruction and subsequent bronchodilatation.

Several aspects of computer-based analysis

There is increasing interest in the measurement of tPTEF/tE as a measure of airway obstruction in infants and young children. This simple and noninvasive test could become a powerful tool in epidemiological studies concerning the determinants of early respiratory morbidity [2, 3]. One of the major problems in tidal breathing analysis is the variability of the tidal breathing pattern. The intraindividual coefficient of variation of the ratio tPTEF/tE ranges from 18.1–26.1% in healthy neonates [5, 9] to 21.8% [6] and 26.5% [12] in school-age children. This large variability of breath-to-breath patterns puts several special requirements on the analysis software of the recording instruments.

Firstly, the number of breaths averaged to give an overall mean parameter for each patient has to be large enough to reach a stable value. When the calculated ratio is not stable, the discriminative value of tPTEF/tE as a measure of airway obstruction will be low. Recently, STOCKS *et al.* [13] showed that probably at least 10–15 breathing curves have to be averaged to reach an acceptable level of repeatability. Tidal breathing computer programs which average less than 10–15 breathing curves may result in a high proportion of infants and children being misclassified as having airway obstruction, or as being at risk for respiratory disease in later life [2, 3].

This study shows how the stability of a mean tPTEF/tE ratio was related to the number of unselected breathing cycles which was averaged (fig. 4). In patients with airflow obstruction (after methacholine) the RC approached the maximum after averaging about 10 sequential breathing cycles. In patients with little (baseline) or no (after salbutamol) airflow obstruction, the tidal breathing pattern was more variable (highest $\sigma^2_{\mathrm{intra}}$). This results in lower levels of stability, indicated by lower RC values. Averaging of 15–20 (baseline), or more (after salbutamol), unselected breathing curves is necessary to reach a stable value in these patients.

The tidal breathing analysis program described here can average up to 250 breaths during one test. In sleeping infants, a relatively unlimited number of breathing cycles can be recorded. Unsedated young children do not tolerate endless recordings. In the present study, it was possible to record at least 20 breathing curves after stabilization of the breathing pattern in unsedated children aged 4–7 yrs. This is in line with former results [12].

Because of the limitation of maximal sample size, other possibilities of increasing the stability of the tPTEF/tE ratio were investigated. The RC values both of the no selection method and the by-eye selection method remained under 0.90 in children without or with only slight airflow obstruction (fig. 5). The stability of the computer-selected ratio was optimal in all degrees of airflow obstruction. The stability of the computer selection method exceeded the stability of the other two methods because of low $\sigma^2_{\mathrm{intra}}$ values.

The computer selection method used the centre 50% of tPTEF/tE values around the median. Figure 5 shows the RC values if other cut-off points had been used. The stability of the ratio would have been equal if, for instance, 6 instead of 10 of the outer values had been deleted. This adaptation in the computer program should be considered when these observations are repeated in other groups of patients.

Secondly, tidal breathing analysis computer programs have to exclude curve selection bias. Selection bias is probably inevitable when the investigator selects the curves from the recordings by eye. Several authors report that they selected "regular" curves [5, 6, 10]. Others selected a period of the recording by excluding "technical alterations" of the regular breathing pattern, such as sighs, hiccups and swallowing [2, 3, 12, 13]. Although the use of a well-described selection protocol can lead to good interobserver correlation [12], selection bias can influence the applicability of tidal breathing analysis by new investigators, especially when it is combined with a small number of averaged curves. In the present study, the selection of curves was completely computerized; this ruled out selection bias by the investigator.

The third advantage is that the on-line data processing by the program easily indicates when the tidal breathing pattern is stabilized after starting the recording.

STOCKS *et al.* [13] showed that the first sample of tidal breathing curves after application of the face mask has lower tPTEF/tE values compared to samples during later recordings. Different samples during prolonged recording showed quite stable tPTEF/tE values. The computer program displays the momentary mean tPTEF/tE and VPTEF/VE values during recording of tidal breathing. It is easy to see when these momentary mean values do not change any more during continuation of the recording. In the present study, the adaptation period was generally 20–30 s. We only used tPTEF/tE values which were sampled after this period.

An additional advantage of the use of the computer program is that the time of the recording can be kept to the minimum. The recording can be started immediately after the adaptation period, and the investigator does not spend time in hesitating about whether individual breathing curves are "valid" or "invalid". Minimizing the procedure time increases patient compliance and improves the applicability of the method in large scale epidemiological research.

In conclusion, automatic analysis of tidal breathing flow patterns enhances the applicability as a measure of airflow obstruction. An appropriate computer program can avoid curve selection bias, can produce a stable average of an appreciable number of single curves and allows recording after stabilization of tidal breathing. This study showed that the on-line computer analysis is preferable to the no selection and to the by-eye selection methods.

After resolving these methodological problems, more studies on the value and physiological background of tPTEF/tE have to be performed. The present study shows that in groups of patients tPTEF/tE correlates with airway obstruction.

Acknowledgements: The authors thank M. Diederick-Zwijnenburg and R. Sleegers for their skilful assistance in performing lung function assessment. They thank the Jaeger Corporation for supplying the tidal breathing analysis computer program.

References

1. Mikkilineni S. On tidal expiratory flow measurements in infants (Editorial). *Pediatr Pulmonol* 1994; 18: 71–72.
2. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. Diminished lung function as a predisposing factor for wheezing respiratory illnesses in infants. *N Engl J Med* 1988; 319: 1112–1117.
3. Martinez FD, Morgan WJ, Wright AL, Holberg C, Taussig LM. Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. *Am Rev Respir Dis* 1991; 143: 312–316.
4. Carlsen KH, Lodrup KC. Tidal flow volume loops in the assessment of reversibility to salbutamol in preschool children with and without asthma. *Eur Respir J* 1992; 5: 276s.
5. Lodrup-Carlsen KC, Carlsen KH. Lung function in awake healthy infants: the first five days of life. *Eur Respir J* 1993; 6: 1496–1500.
6. Cutrera R, Filtchev SI, Merolla R, Willim G, Haluszka J, Ronchetti R. Analysis of expiratory pattern for monitoring bronchial obstruction in school-age children. *Pediatr Pulmonol* 1991; 10: 6–10.
7. Stocks J, Jackson E, Gappa M, Mukhtar Z, Costeloe K, Dezateux C. Analysis of tidal expiration: how stable is TME/TE? *Eur Respir J* 1992; 5: 38s.
8. Lodrup KC, Mowinckel P, Carlsen KH. Lung function measurements in awake compared to sleeping newborn infants. *Pediatr Pulmonol* 1992; 12: 99–104.
9. Lodrup-Carlsen KC, Magnus P, Carlsen KH. Lung function by tidal breathing in awake healthy newborn infants. *Eur Respir J* 1994; 7: 1660–1668.
10. Clarke JR, Aston H, Silverman M. Evaluation of a tidal expiratory flow index in healthy and diseased infants. *Pediatr Pulmonol* 1994; 17: 285–290.
11. Aston H, Clarke J, Silverman M. Are tidal breathing indices useful in infant bronchial challenge tests? *Pediatr Pulmonol* 1994; 17: 225–230.
12. Van der Ent CK, Brackel HJL, Van der Laag J, Bogaard JM. Tidal breathing analysis as a measure of airway obstruction in children aged three years and over. *Am J Respir Crit Care Med* 1996; 153: 1253–1258.
13. Stocks J, Dezateux CA, Jackson EA, Hoo A, Costeloe KL, Wade AM. Analysis of tidal breathing parameters in infancy: how variable is tPTEF/tE? *Am J Respir Crit Care Med* 1994; 150: 1347–1354.
14. Carlsen KH, Lodrup-Carlsen KC. Tidal breathing analysis and response to salbutamol in awake young children with and without asthma. *Eur Respir J* 1994; 7: 2154–2159.
15. Kay AB, Holgate ST. International consensus report on diagnosis and management of asthma. *Clin Exp Allergy* 1992; 22 (Suppl. 1): 1–5.
16. American Thoracic Society. Standardization of spirometry: 1987 update. *Am Rev Respir Dis* 1987; 136: 1285–1298.
17. Zapletal A, Paul T, Samanek M. Die Bedeutung heutiger Methoden der Lungenfunktions Diagnoshk zur Feststellung einer Obstruktion der Atemwege bei Kindern und Jugendlichen. *Z Erkr Atmorg* 1977; 149: 343–371.
18. Wilts M, Hop WCJ, Van der Heyden GHC, Kerrebijn KF, De Jongste J. Measurements of bronchial responsiveness in young children: comparison of transcutaneous oxygen tension and functional residual capacity during induced bronchoconstriction and -dilatation. *Pediatr Pulmonol* 1992; 12: 181–185.
19. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; i: 307–310.