

# Tidal breathing parameters in the first week of life and subsequent cough and wheeze

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## Abstract

**Background** – Assessment of tidal breathing parameters may be a useful method of predicting respiratory problems in early childhood. Low values of  $T_{PTEF}/T_E$  (the ratio of the proportion of time to reach peak tidal expiratory flow to total expiratory time) outside the neonatal period have been significantly related to respiratory tract illness with wheezing in boys in the first year of life.

**Methods** –  $T_{PTEF}/T_E$  measurements in the perinatal period were evaluated in non-sedated infants and the predictive value of this early measurement for subsequent respiratory morbidity during infancy was assessed. Flow during tidal breathing was measured while the infant slept quietly in a plethysmograph using a Fleisch pneumotachograph inserted into an infant face mask. Recruitment continued until traces from 60 infants with 10 consecutive flow curves without artefacts were obtained. In addition, plethysmographic measurements of airway resistance ( $R_{aw}$ ) and thoracic gas volume (TGV) were measured and specific conductance (sGaw) calculated. Parents recorded their infant's cough and wheeze during the first 12 months of life.

**Results** – Sixty five measurements were made in 60 infants with a mean age of two days and gestational age of 40 weeks. Two observers separately calculated  $T_{PTEF}/T_E$  ratios on 25 traces randomly selected from the pool of 60. The mean difference between the two observers was  $-0.004$  (limits of agreement 0.048 to  $-0.056$ ). Thirteen infants became symptomatic (wheeze, with or without cough); their median  $T_{PTEF}/T_E$  ratio (0.349) was significantly lower than the rest of the cohort (median 0.412) and they also had significantly higher  $R_{aw}$  and lower sGaw. The positive predictive value of a low  $T_{PTEF}/T_E$  ratio, however, was only 41%.

**Conclusions** – These results suggest that the use of this test in the prediction of future respiratory disease in an individual is limited.

(*Thorax* 1996;51:815-818)

Keywords: infancy, tidal breathing parameters.

applied appropriately. The results of airway resistance ( $R_{aw}$ ) measurements are useful but may require the patient to be sedated.<sup>1</sup> A technique to measure tidal breathing parameters (the proportion of time to reach peak tidal expiratory flow to total expiratory time ( $T_{PTEF}/T_E$  ratio)), previously used in adults,<sup>2</sup> has recently been employed in infants, some of whom were not sedated. Martinez *et al*<sup>3</sup> reported that boys who later developed lower respiratory tract illness with wheezing had significantly lower values of  $T_{PTEF}/T_E$  at the mean age of approximately two months. Assessment of lung function at that age, however, necessitates recalling infants to hospital and is thus difficult to apply universally. We felt it important to assess whether measurement of  $T_{PTEF}/T_E$  in the first week of life, when infants are still in hospital with their mothers, provided a useful prediction of subsequent respiratory morbidity and whether such a relationship, as previously described,<sup>3</sup> was dependent upon sex.

## Methods

Infants were eligible for entry into the study if they had no congenital anomalies, were born at term, and had no respiratory problems in the immediate perinatal period. Infants who fulfilled the eligibility criteria were recruited from an ongoing study examining the effects of first trimester antenatal investigations which were being undertaken because of maternal age or parental anxiety. In that study lung function measurements were made in the first week of life and the infants were subsequently followed until at least one year of age. The parents kept diary cards on which the presence of respiratory symptoms (wheeze and cough) were recorded. They were contacted on two separate occasions and the infant's symptoms were retrospectively reviewed from birth to the first contact and between the first and second contact, respectively. The follow up study was approved by the King's College Hospital ethics committee and parents gave informed consent before entry into the study.

Infants were seen in the Paediatric Respiratory Laboratory. Lung function measurements were made 30-60 minutes after a feed during quiet sleep without sedation. The infants were studied in the supine position lying in a whole body plethysmograph. Tidal breathing parameters were measured before estimation of thoracic gas volume and airway resistance. Flow during tidal breathing was measured while the neonate breathed through an infant

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Received 13 July 1995  
Returned to authors  
29 September 1995  
Revised version received  
19 February 1996  
Accepted for publication  
7 March 1996

Respiratory problems are common during infancy. Accurate predictive tools are therefore desirable so that intervention strategies can be

face mask. The mask was connected to a rebreathing bag via a heated Fleisch pneumotachograph and was sealed around the infant's nose and mouth using silicone putty to ensure an airtight seal. The dead space of the equipment was 15 ml. The flow signal was calibrated with a rotameter and was linear between zero and 12 l/min. Flow and volume signals were collected on ultraviolet sensitive paper. The shape of the tidal breathing expiratory curve was studied. The time to reach peak (maximum) tidal expiratory flow ( $T_{PTEF}/T_E$ ) as a proportion of total expiratory time ( $T_E$ ) was measured. The mean  $T_{PTEF}/T_E$  ratio was calculated from the first 10 regular breaths. Recruitment continued until 60 suitable traces – that is, with 10 consecutive flow curves without artefacts – were obtained.

Thoracic gas volume (TGV) and airway resistance ( $R_{aw}$ ) were measured using a whole body plethysmograph (Hammersmith Hospital, Department of Medical Engineering, London, UK) with a total volume of 90 litres. The infant breathed through a face mask which was connected to the rebreathing bag via a heated pneumotachograph. The face mask was sealed around the infant's nose and mouth using silicone putty to ensure an airtight seal. The infant breathed through a heated, humidified rebreathing system to avoid box pressure changes due to heating and cooling of respired gas. TGV was measured at the end of normal inspiration and  $R_{aw}$  at two thirds of maximum inspiratory flow using the techniques of Dubois *et al* suitably modified for infants.<sup>4,5</sup> TGV was calculated from five breaths during occlusion and the reported value was adjusted to end expiratory lung volume; five separate occlusions were made.  $R_{aw}$  was calculated from 10 breaths. Measurements were corrected for the apparatus dead space which included the face mask (15 ml) and its resistance (8 cm  $H_2O/l/s$ ) measured at flows of between 5 and 15 l/min. The calibration of the plethysmograph was performed as described previously.<sup>6</sup>

An observer who was unaware of the results of the  $T_{PTEF}/T_E$  measurements evaluated the diary cards. Infants were defined as symptomatic if they wheezed, with or without cough, for more than one day following a respiratory tract infection or wheezed for at least 24 hours without any respiratory tract infection.

#### STATISTICAL ANALYSIS

To determine the interobserver repeatability of the measurements, 25 traces were randomly selected and the mean  $T_{PTEF}/T_E$  ratio for each trace was calculated separately by two observers. The coefficient of variation (CV) was determined for each trace by each observer. The coefficient of repeatability between the two observers' results was calculated according to the method of Bland and Altman.<sup>7</sup> Differences between groups were assessed for statistical significance using the Mann-Whitney U test. The sensitivity, specificity, and positive predictive value for the development of respiratory symptoms in the first year of life of the median  $T_{PTEF}/T_E$  of the study population were calculated.

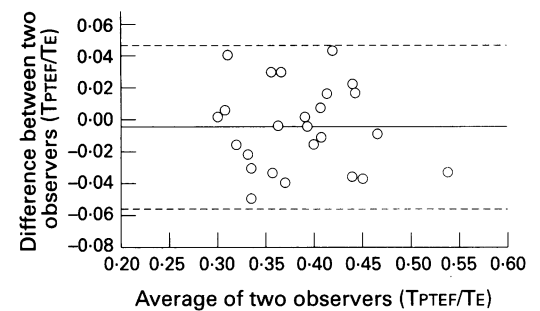


Figure 1 Differences between the two observers in the  $T_{PTEF}/T_E$  ratio of an individual plotted against the mean  $T_{PTEF}/T_E$ . The mean difference and 95% confidence intervals of the mean are demonstrated (solid and broken lines, respectively).

#### Results

Lung function measurements were carried out in 65 neonates, but in five cases the traces were unsuitable for analysis. Results were used from the remaining 60 neonates (25 boys) who were born at a median gestational age of 40 weeks (range 37–42) and had a birth weight of 3400 g (range 1800–4960). The median age at the time of investigation was two days (range 1–12). The ethnic origin of the neonates was Caucasian in 42 cases, Afro-Caribbean in 12, Asian in one, and mixed in five. The mean (SD)  $T_{PTEF}/T_E$  values of the two observers were 0.383 (0.058) and 0.387 (0.06), respectively, and the mean (SD) difference between paired measurements was  $-0.004$  (0.026). The mean (SD) coefficient of variation was 20.4 (8.8)% (range 3–41) for observer 1 and 15.3 (6.6)% (range 6–31) for observer 2. The coefficient of repeatability of the  $T_{PTEF}/T_E$  results was 0.052 with limits of agreement of 0.048 to  $-0.056$  (fig 1).

Thirteen infants (four boys) were symptomatic at follow up (fig 2). They did not differ from the other 47 with respect to their birth weight, the proportion who were growth retarded, their postnatal age, mode of delivery, ethnic origin, family history of atopy, or respiratory rate (table 1). The median  $T_{PTEF}/T_E$  of the symptomatic group, however, was significantly different from that of the non-symptomatic infants, as was their airway resistance and specific conductance but not their thoracic gas volume ( $p < 0.01$ ) (table 1). In the total group of 60 neonates there was no significant difference between the median  $T_{PTEF}/T_E$  of the boys (0.400, range 0.298–0.477) and the

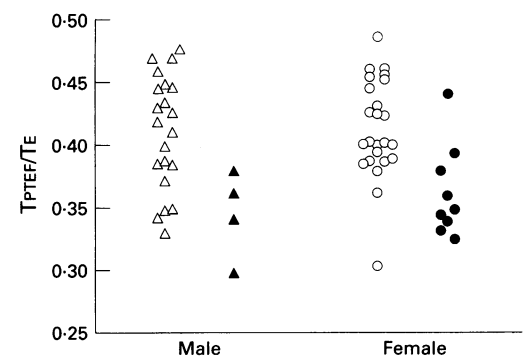


Figure 2 Individual  $T_{PTEF}/T_E$  results for boys ( $\Delta$  = non-symptomatic,  $\blacktriangle$  = symptomatic) and girls ( $\circ$  = non-symptomatic,  $\bullet$  = symptomatic).

Table 1 Comparison of symptomatic and asymptomatic infants

	Symptomatic	Asymptomatic
n	13	47
Birth weight (g)	3540 (2400–4830)	3370 (1800–4960)
Intrauterine growth retardation	2 (15)	6 (13)
Postnatal age (days)	3 (1–10)	2 (1–12)
Vaginal delivery (SVD)	9 (69)	38 (80)
Caucasian	9 (69)	33 (70)
Family history of atopy	5 (38) (2 boys/3 girls)	15 (32) (6 boys/9 girls)
Respiratory rate (breaths/minute)	62 (38–93)	61 (39–85)
TPTEF/TE	0.349 (0.298–0.442)	0.412 (0.303–0.520)
TGV (ml/kg)	34 (25–43)	33 (22–44)
Raw (cm H <sub>2</sub> O/l/s)	30 (25–43)	25 (15–39)
sGaw (cm H <sub>2</sub> O/s)	0.285 (0.210–0.397)	0.389 (0.224–0.547)

Results are presented as median (range) or no. (%).

TPTEF/TE = time to reach peak tidal expiratory flow to total expiratory time; TGV = thoracic gas volume; Raw = airway resistance; sGaw = specific airway conductance.

Table 2 Prediction of persistence of respiratory symptoms at one year using a TPTEF/TE ratio of &lt; 0.4

	Boys	Girls
Sensitivity (%)	100	89
Specificity (%)	62	65
Positive predictive value (%)	33	47
Negative predictive value (%)	100	94

girls (0.398, range 0.303–0.520). Symptomatic boys and girls had lower TPTEF/TE ratios than non-symptomatic boys and girls, respectively ( $p < 0.02$ ). A TPTEF/TE ratio of less than 0.4 had a 92% sensitivity, 64% specificity, and 41% positive predictive value for respiratory symptoms in infancy. Similar values were obtained when boys and girls were considered separately (table 2).

## Discussion

This study has shown that the TPTEF/TE ratio measured during the first week of life in infants who subsequently developed respiratory symptoms was lower than in those who remained asymptomatic. This difference was particularly apparent in boys. These results are compatible with earlier findings in infants examined at a mean age of two months,<sup>3</sup> but the average TPTEF/TE of our study population was higher than that reported by Martinez *et al.*<sup>3</sup> Carlsen *et al.*,<sup>8,9</sup> however, have demonstrated a decrease in TPTEF/TE with increasing postnatal age during the first week of life. A review of the published data (table 3) shows that the trend persists over the first few months of life. The TPTEF/TE results we report are in keeping with both the findings of Carlsen *et al.*<sup>8</sup> and Stick *et al.*<sup>10</sup> The latter group measured TPTEF/TE using a

similar technique to that employed in the present study and, in addition, used respiratory inductance plethysmography (Respirtrace).

The variability in measurements of TPTEF/TE was high, despite excluding 10% of traces as unsuitable for analysis. It has recently been suggested that at least 20 breaths (from two separate epochs) should be analysed to obtain a more representative value of TPTEF/TE.<sup>11</sup> Others have used a mean of 3–8 runs of five sequential breaths<sup>12</sup> but analysis of 10 consecutive tidal breaths has been undertaken more commonly.<sup>3,13,14</sup> As a consequence, we chose the latter method. Our intraindividual variation is similar to that of Carlsen *et al.*,<sup>8</sup> but both results compare unfavourably with those of Stick *et al.*<sup>10</sup> It seems unlikely, however, that this high variability is due to measurement technique as Stick quotes similar results using a face mask and pneumotachograph or a Respirtrace. The high variability may be explained by the low postnatal age of our patients.<sup>11</sup> Despite this, however, we were able to demonstrate significant differences between groups. Our study population containing 13 symptomatic infants, given the coefficient of variation of the measurement we noted, allowed us to detect a difference in TPTEF/TE of 0.066 between the groups with 80% power at the 5% level, which is below the difference reported in prospective studies.<sup>3,13</sup> The positive predictive value of a low TPTEF/TE was relatively poor, however, but our symptomatic group consisted of only 13 infants and obstructive airway disease in early childhood is multifactorial so one factor alone could not be expected to have a high predictive value.

Infants who subsequently became symptomatic could not be identified by their birth weight, the proportion who were growth retarded, their postnatal age, mode of delivery, ethnic origin, or family history of atopy (table 1). As the numbers of symptomatic infants were small we did not attempt to subdivide the group according to the severity of their symptoms, so we cannot exclude that there may have been clinically important differences between these groups and the controls. The respiratory rate of the two groups did not differ significantly and was comparable to that reported by Carlsen *et al.*<sup>8</sup> We found a 16% difference in the TPTEF/TE ratio between subsequently symptomatic and asymptomatic

Table 3 Previously published results of TPTEF/TE ratio

Author	TPTEF/TE	Mean approximate postnatal age of study group	Mean respiratory rate (bpm)
Carlsen <i>et al.</i> <sup>8</sup>	0.39	One day	58.9 (25–114)
Stick <i>et al.</i> <sup>10</sup>	0.423–0.427	58 hours (33–114)	47.9–46.9
Stocks <i>et al.</i> <sup>11</sup>	0.4	Neonates (< 2 weeks)	Not given
Clarke <i>et al.</i> <sup>12</sup>	0.38	One month	62
Clarke <i>et al.</i> <sup>18</sup>	0.39 (boys) 0.41 (girls)	Neonates	Not given
Stocks <i>et al.</i> <sup>11</sup>	0.29	Six weeks	Not given
Young <i>et al.</i> <sup>13</sup>	0.39 (0.254 in flow limited infants)	One month	42
Dezateux <i>et al.</i> <sup>15</sup>	0.321	8 weeks	46.5
Martinez <i>et al.</i> <sup>3</sup>	0.312 (0.254 in wheezing infants)	8 weeks	Not given
Martinez <i>et al.</i> <sup>14</sup>	0.297	8 weeks	Not given
Dezateux <i>et al.</i> <sup>15</sup>	0.295	50 weeks	30.5
Stocks <i>et al.</i> <sup>11</sup>	0.27	One year	Not given
Clarke <i>et al.</i> <sup>11</sup>	0.29	One year	29

\*Two techniques of measuring TPTEF/TE were employed.

infants, which is similar to the 19% difference reported by Martinez *et al.*<sup>3</sup> Clarke *et al.*,<sup>12</sup> however, found no significant differences between groups, but their population all had a parental history of atopy which may have masked differences.

In older children and adults the shape of the tidal breathing expiratory flow-time curve, quantified by calculation of  $TP_{TEF}/TE$ , is closely correlated with specific airway conductance ( $sGaw$ )<sup>2</sup> – that is, the reciprocal of airway flow resistance divided by lung volume. A relationship between  $TP_{TEF}/TE$  and  $sGaw$  has also been noted in infants older, but not younger, than three months by Dezateux *et al.*<sup>15</sup> who suggested that, in the younger infants, the pattern of expiratory flow may reflect dynamic maintenance of FRC as much as a response to airway calibre, hence the lack of a significant relationship between the  $TP_{TEF}/TE$  ratio and  $sGaw$  in such patients. Interestingly, in this study we found the symptomatic infants to have significantly lower  $TP_{TEF}/TE$  ratios and specific conductance. Low  $TP_{TEF}/TE$  ratios have been found in patients with obstructive lung disease<sup>2</sup> and bronchopulmonary dysplasia.<sup>16</sup> Martinez *et al.* found that boys with low  $TP_{TEF}/TE$  values had a greatly increased risk of having a wheezing illness in the first year of life;<sup>3</sup> in addition, those who wheezed during the first year of life and had at least one additional lower respiratory illness had lower initial levels of  $TP_{TEF}/TE$  and conductance than “never” wheezers.<sup>14</sup> It was suggested that lower levels of airway conductance predispose, not to infection, but to clinically relevant airway obstruction following a suitable stimulus.<sup>14</sup> Clarke *et al.*<sup>12</sup> recently failed to demonstrate a significant difference in tidal breathing parameters between infants who subsequently developed lower respiratory symptoms of cough or wheeze and those who did not. Their population, however, differed from that of the present or earlier study<sup>3</sup> as only infants of atopic parents were included and this may have influenced the results. In both our study and that of Martinez *et al.*<sup>3</sup> a sex bias was found. Although this might suggest that boys have smaller airways relative to lung size than girls,<sup>17</sup> we did not find a significant difference in the  $TP_{TEF}/TE$  ratio between boys and girls but this is in contrast to an earlier report.<sup>8</sup> With our study population of only 60, however, a type II error cannot be excluded.

Our findings demonstrate the feasibility of measuring the  $TP_{TEF}/TE$  ratio in the perinatal period in non-sedated infants. The positive predictive value of a low  $TP_{TEF}/TE$ , however, was low and, if this result is confirmed in future

studies, it undermines the usefulness of tidal breathing parameters as criteria for intervention strategies in an individual. Although a high variability in the measurement was noted, we were able to find statistically significant differences between infants who were subsequently symptomatic or asymptomatic and this technique may therefore be appropriate for large population studies.

Dr B Yuksel is supported by the Medical Research Council and Dr F Giffin by the Children Nationwide Medical Research Fund.

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