Tidal breathing flow measurement in awake young children by using impedance pneumography

Ville-Pekka Seppä,1 Anna S. Pelkonen,2 Anne Kotaniemi-Syrjänen,2 Mika J. Mäkelä,2 Jari Viik,1 and L. Pekka Malmberg2

1Department of Electronics and Communications Engineering, Tampere University of Technology, Tampere, Finland; and 2Department of Allergology, University Central Hospital, Helsinki, Finland

Submitted 6 June 2013; accepted in final form 30 September 2013

Seppä V-P, Pelkonen AS, Kotaniemi-Syrjänen A, Mäkelä J, Viik J, Malmberg LP. Tidal breathing flow measurement in awake young children by using impedance pneumography. J Appl Physiol 115: 1725–1731, 2013. First published October 3, 2013; doi:10.1152/japplphysiol.00657.2013.—Characteristics of tidal breathing (TB) relate to lung function and may be assessed even in young children. Thus far, the accuracy of impedance pneumography (IP) in recording TB flows in young children with or without bronchial obstruction had not been evaluated. The aim of this study was to evaluate the agreement between IP and direct flow measurement with pneumotachograph (PNT) in assessing TB flow and flow-derived indices relating to airway obstruction in young children. Tidal flow was recorded for 1 min simultaneously with IP and PNT during different phases of a bronchial challenge test with methacholine in 21 wheezy children aged 3 to 7 years. The agreement of IP with PNT was found to be excellent in direct flow signal comparison, the mean deviation from linearity ranging from 2.4 to 3.1% of tidal peak inspiratory flow. Methacholine-induced bronchoconstriction or consecutive bronchodilation induced only minor changes in the agreement. Between IP and PNT, the obstruction-related tidal flow indices were equally repeatable, and agreement was found to be high, with intraclass correlation coefficients for TPEF/TV, VPEF/VE, and parameter S being 0.94, 0.91, and 0.68, respectively. Methacholine-induced changes in tidal flow indices showed significant associations with changes in mechanical impedance of the respiratory system assessed by the oscillometric technique, with the highest correlation found in VPEF/VE ($r = -0.54$; $P < 0.005$ and $r = -0.55$; $P < 0.005$ by using IP or PNT, respectively). The results indicate that IP can be considered as a valid method for recording tidal airflow profiles in young children with wheezing disorders.

Lung function assessment of preschool children is hindered by their limited cooperation in conventional tests such as peak expiratory flow (PEF) or spirometry, and the methods available for younger children are laborious and time-consuming. However, indices derived from spontaneous tidal respiratory air flow and the shape of tidal expiratory flow-volume and flow-time curves relate to lung function such as forced expiratory volume in 1 s (FEV1) (3) or airway resistance (18), and they are easier to record even in young children. As a more advanced approach, the time dynamics and complexity properties of the tidal air flow signal have been analyzed and found to relate to various respiratory conditions (7, 9, 22, 30, 34). These analyses require accurate recording of tidal air flow profiles, which thus far has been possible primarily in a laboratory setting directly from the mouth with a pneumotachograph for limited time periods (2).

Recently, a novel option for assessing tidal flow has emerged as a result of development in signal processing of impedance pneumography (IP) (26), which records continuous lung volume changes through skin electrodes. This method has shown excellent pulmonary flow signal waveform agreement in healthy adults in a laboratory setting (25, 27), and has additional potential advantages by avoiding interference with breathing pattern by a pneumotachograph and enabling tidal flow measurement in an ambulatory long-term setting; for instance, overnight at home. There are, however, no previous data on the accuracy of IP in tidal flow measurement of young children with or without airflow obstruction. Age-dependent changes in regional ventilation (4), ventilation-perfusion mismatch during obstructive episodes of asthma (21), and irregular breathing patterns of awake, noncooperative young children may potentially compromise the linear behavior of airflow signal recorded with IP. This study presents for the first time a thorough analysis on the accuracy of IP in tidal flow assessment in young children in an experimental design, including induced bronchoconstriction.

The primary objective of this work was to study the agreement between IP and a direct mouth pneumotachograph (PNT) in tidal flow measurement in preschool children. The agreement was assessed at baseline conditions and during methacholine-induced bronchoconstriction (MB). As the secondary aim, the changes in tidal flow characteristics during MB were compared with mechanical impedance measurements of the respiratory system by using an oscillometric technique.

MATERIALS AND METHODS

Patients and clinical procedure. The study subjects included 21 children aged 3–7 years who were referred to the Pediatric Unit of the Department of Allergology, Helsinki University Central Hospital because of recurrent or persistent lower respiratory tract symptoms (wheeze, cough, and/or shortness of breath). The baseline characteristics of the children are presented in Table 1. Most (90%) children were born full term. Two prematurely born children had a history of very low birth weight (<1,500 g). At the time of testing, none of the children had experienced a respiratory tract infection in the preceding 2 wk. One child used oral montelukast and one child used inhaled budesonide at the time of testing, and the other children were without regular medication. Short-acting $B_2$-agonists were withheld for at least 12 h preceding the test. The study was approved by the institutional pediatric ethics committee of Helsinki University Central Hospital.

The design of the study included simultaneous recordings of tidal breathing (TB) by using a PNT and IP lasting at least 60 s in a sitting position. The recordings were repeated at baseline before and after the
lungs function measurements with oscillometry, during MIB, and 10 min after inhalation of a bronchodilator (BRD).

**Lung function measurements.** For tidal flow recordings, the flow was measured at the airway opening via a mouthpiece by using a calibrated, heated, Lilly-type PNT (Masterscreen PFT; Jaeger, Germany) with a dead space of 90 ml. A nose clip was used, and the child was in a sitting position. After body temperature pressure saturated correction, data were digitized with a sampling frequency of 100 Hz and later oversampled to 256 Hz to match the IP recording. Real-time visualization of the PNT signal was used to ensure stable and regular respiratory breathing pattern before the start of recording (2).

The methodology of lung function measurements by using the oscillometric technique has been previously described in detail (16). The output pressure and flow signals were analyzed for their amplitude and phase difference to determine the resistance (Rrs) and reactance (Xrs) of the respiratory system, both components of the respiratory impedance (Zrs). During the measurement, the child was in a sitting position, breathing quietly through a mouthpiece. A nose clip was used and the cheeks were supported by the hands of the investigator. Measurements were repeated to obtain three acceptable data sets at baseline, and two acceptable data sets at each time point. The parameters of interest in this study were respiratory impedance and respiratory reactance at 5 Hz (Rrs5 and Xrs5, respectively), and the total respiratory impedance at 5 Hz (Zrs5).

A dosimetric bronchial provocation test adjusted for preschool children was applied (14). After baseline measurements of Rrs5, increasing doses of methacholine chloride were administered by using an inhalation-synchronized dosimeter (Spira Electro 2; Spira Respiratory Care Centre, Hämeenlinna, Finland) connected to a calibrated nebulizer (Salter Labs 8900; Arvin, CA), and after each dose, Rrs5 was remeasured. The procedure included five dose steps (15, 60, 210, 660, and 2,010 μg), and was continued until a 40% increase in Rrs5 was observed or the maximum dose of methacholine was administered. After the final measurement of Rrs5, TB measurements were recorded. The provocative dose of methacholine causing a 40% fall in Rrs5 (PD0.40 Rrs5) was determined from the dose-response curves. Following the challenge test, the children received inhaled salbutamol (0.3 mg, 0.1 mg/dose; Ventoline Evohaler; GlaxoSmithKline, Middlesex, UK) via Babyhaler (GlaxoSmithKline, Brentford, UK), and the measurement of Rrs5 was repeated 15 min after salbutamol inhalation.

**Impedance pneumography.** In IP, the electrical impedance of the thorax is measured by feeding a small, high-frequency current, I, through one electrode pair and measuring the resulting voltage signal, U, by another electrode pair. The electrical impedance, Z = U/I, increases as air enters the lungs during inspiration and decreases with expiration. The resulting volume-oriented signal can be differentiated to obtain a flow rate signal (28). IP does not enable measuring absolute values of flow rate as milliliters per second (ml/s) because the intersubject and interposture variation in the ratio of impedance change, ΔZ, to volume change, ΔV, is rather large (28). However, using correct electrode placement, the ΔZ/ΔV ratio is highly linear, which is the satisfactory property for almost all types of tidal air flow analysis. Here the current feeding electrodes were placed on both sides of the thorax on the midaxillary line at the height of the fifth intercostal space and the voltage measurement electrodes on the arms opposing the other electrode pair. This configuration has been shown to establish a highly linear ΔZ/ΔV ratio in healthy adults (24). The distortive impedance oscillations resulting from cardiac activity were removed by a filtering technique developed for this purpose (26). IP and electrocardiogram (ECG) signals were recorded and stored at a 256-Hz sampling rate by a small device of our own construct, similar to the one presented by Vuorela et al. (31) using normal Ag-AgCl ECG electrodes (Blue Sensor P; Ambu, Ballerup, Denmark). Because the conventional four-electrode IP is susceptible to motion artifact, the recorded signals were visually inspected for motion distortions and those segments were discarded.

**Tidal breathing indices used for assessment of airflow obstruction.** Tidal respiratory flow was quantified by parameters \( T_{\text{PTEF}}/T_E \), \( V_{\text{PTEF}}/V_E \), and the parameter S introduced by Williams et al. (32), as defined in the European Respiratory Society and American Thoracic Society statement (2) and illustrated in Fig. 1. From each 1-min recording, the parameters were determined by manually extracting a segment of regular breathing containing at least four consecutive breaths. If no such segment could be found, the recording was excluded from the analysis. Here the current feeding electrodes were placed on both sides of the thorax on the midaxillary line at the height of the fifth intercostal space and the voltage measurement electrodes on the arms opposing the other electrode pair. This configuration has been shown to establish a highly linear ΔZ/ΔV ratio in healthy adults (24). The distortive impedance oscillations resulting from cardiac activity were removed by a filtering technique developed for this purpose (26). IP and electrocardiogram (ECG) signals were recorded and stored at a 256-Hz sampling rate by a small device of our own construct, similar to the one presented by Vuorela et al. (31) using normal Ag-AgCl ECG electrodes (Blue Sensor P; Ambu, Ballerup, Denmark). Because the conventional four-electrode IP is susceptible to motion artifact, the recorded signals were visually inspected for motion distortions and those segments were discarded.

![Fig. 1. Illustration of the three tidal breathing parameters \( T_{\text{PTEF}}/T_E \), \( V_{\text{PTEF}}/V_E \), and S. PTEF denotes peak tidal expiratory flow. \( T_{\text{PTEF}}/T_E \) is defined as the ratio of time to reach PTEF to total duration of expiration. \( V_{\text{PTEF}}/V_E \) is defined as the ratio of volume expired at time of PTEF to total expired volume. S is defined in the post-PTEF part of the flow-time curve (light gray background) by normalizing the flow and time range to 0...100 and fitting a line as \( \text{flow}(t) = St + b \), where \( t \) is time.](http://jap.physiology.org/)

---

**Table 1. Characteristics of the study children**

<table>
<thead>
<tr>
<th>Study children, n</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys, n (%)</td>
<td>16 (76)</td>
</tr>
<tr>
<td>Gestational age, median (range), wk</td>
<td>40 (27–42)</td>
</tr>
<tr>
<td>Birthweight, median (range), g</td>
<td>3,500 (980–4,770)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>6.0 (3.6–7.9)</td>
</tr>
<tr>
<td>Height, median (range), cm</td>
<td>118 (99–125)</td>
</tr>
<tr>
<td>Weight, median (range), kg</td>
<td>21.5 (15.5–31.8)</td>
</tr>
<tr>
<td>Skin prick test positive, n (%)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Allergic rhinitis, n (%)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Atopic eczema, n (%)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Parental asthma, n (%)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Wheeze, n (%)</td>
<td>21 (100)</td>
</tr>
<tr>
<td>Parental smoking, n (%)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Parental asthma, n (%)</td>
<td>11 (52)</td>
</tr>
<tr>
<td>Baseline Rrs5, median (range), kPa·1−1·s−1</td>
<td>0.77 (0.54–1.84)</td>
</tr>
<tr>
<td>Baseline Xrs5, median (range), kPa·1−1·s−1</td>
<td>−0.20 (−0.10–0.50)</td>
</tr>
<tr>
<td>Baseline Rrs5, median (range), z-score</td>
<td>−0.46 (−2.47–5.48)</td>
</tr>
<tr>
<td>Baseline Xrs5, median (range), z-score</td>
<td>0.68 (−4.27–2.41)</td>
</tr>
</tbody>
</table>

Rrs5, respiratory resistance at 5 Hz; Xrs5, respiratory reactance at 5 Hz.
analysis. The TB parameters were derived from each breath and averaged for each recording with trimmed mean that rejected the highest and lowest 5% of values. Putatively, \( T_{PTEF} \), \( V_{max}/V_{res} \), and the parameter \( S \) should decrease as a result of bronchial obstruction (MIB phase), and increase after bronchodilation (BRD phase).

**Statistical analysis.** The agreement between IP flow signal, \( V_{IP} \), and PNT flow signal, \( V_{PNT} \), for each measurement was analyzed in two ways. First by forming the sample-by-sample absolute difference signal as \( d(n) = |V_{PNT}(n) - V_{IP}(n)|, n = 1 \ldots m \), where \( n \) is sample number and \( m \) is signal length, and presenting the median of \( d \) for each measurement as \( D_{SS} \). This gives a measure of the average difference between the two signals, but does not contain information on whether the difference is distributed randomly in time or does it relate to the phase of respiration. Considering the analysis of the shapes of the expiratory flow curves for instance, a measurement error distributed randomly can be less deceiving and easier to remove than one that is consistently occurring in the same phase. This motivates the second analysis that reveals the distribution of the differences by plotting the value pairs \( V_{PNT}(n) \) and \( V_{IP}(n) \) for each sample, fitting a line to the distribution, and assessing the distance from the line for each sample, as illustrated in Fig. 2A. Then the distances are divided into \( k \) bins according their respective values of \( V_{PNT}(n) \) and the deviation from linearity of each bin \( m \) is represented by the median of the distances in it as \( D_{bin,m} \) (Fig. 2A). The average deviation from linearity, \( D_{median} \), is then defined as the mean of all \( D_{bin,m} \). For each measurement the \( V_{IP} \) and \( V_{PNT} \) signals were normalized such that 100% flow means the median tidal peak inspiratory flow (TPIF) encountered during that measurement. Bins containing less than 2% of the samples of a measurement were discarded from the analysis.

The repeatability of TB indices was determined by using the paired recordings at the baseline. Within-subject standard deviation, \( SD_{SS} \), was calculated for each patient for each of the baseline variables as \( SD_{SS} = \frac{1}{n} \sum_{i=1}^{n} (X_{BL1,i} - X_{BL2,i})^2 \) where \( X \) is the measured value obtained during first and second baseline measurement, BL1 and BL2, respectively. MIB and BRD induced changes in \( Rrs5 \), \( Xrs5 \), and \( Zrs5 \) were assessed and compared with those of the indices of TB flow, assessed either by PNT or IP recordings. Changes in assumed direction that exceeded 1.65 times \( SD_{SS} \) during MIB or BRD, were considered significant.

A two-tailed paired \( t \)-test was used to compare the oscillometric parameters between the test phases and the TB parameters between test phases. Where a \( t \)-test was used, the variables were first tested to have normal distribution using the Kolmogorov-Smirnov test. A paired Wilcoxon signed rank test was used for comparing changes in \( D_{SS} \) and \( D_{t} \) between the test phases and for comparing \( SD_{SS} \) between IP and PNT for each TB parameter. Pearson linear correlation was calculated between oscillometric and TB parameters for changes induced by MIB and BRD. Intraclass correlation coefficient, ICC, was used for assessing the TB parameter agreement between IP and PNT. To relate the difference between IP and PNT to the range of the encountered TB parameter values, the difference was also assessed as intersubject z-scores i.e., by normalizing (dividing) the difference with intersubject standard deviation of the PNT TB parameter.

Statistical analyses were performed using Matlab (version R2012b) and SPSS (version 21) software. Criteria for statistical significance was \( P < 0.05 \).

**RESULTS**

**Lung function of study subjects.** The baseline lung function assessed by impulse oscillometry was abnormal (\( Rrs5 z-score \geq 2 \) SD or \( Xrs5 z-score \leq -2 \) SD) in one child with a history of very low birth weight, and within normal limits in others (16) (Table 1). All except two children responded to methacholine by an increase of \( Rrs5 \) at least 40% having a median \( PD_{40} \) of 129 (20 – 920) \( \mu \)g. Recordings of TB were successful in all the subjects at each time point.

**Agreement between measurement methods.** To evaluate whether the agreement between IP and PNT signals varies with different states of respiratory function, assessments were made separately at the baseline, MIB, and BRD phases. The sample-by-sample differences, \( D_{SS} \), for baselines 1 and 2 (BL1 and BL2), MIB, and BRD phases were (mean ± SD) 5.7 ± 1.2%, 6.7 ± 1.9%, 6.9 ± 1.4%, and 7.5 ± 2.0% of TPIF, respectively. When comparing \( D_{SS} \) between the phases of the study a statistically significant change in \( D_{SS} \) was obtained between the mean of BL1 and BL2 vs. BRD (\( P = 0.003 \)), but not vs. MIB (\( P = 0.277 \)). \( D_{SS} \) did not correlate with the degree of airway obstruction, assessed by \( z \) scores of any of the oscillometric measures (\( P > 0.35 \) for all).

The average deviation from linearity, \( D_{median} \), for BL1, BL2, MIB, and BRD phases were (mean ± SD) 2.4 ± 1.0%, 3.0 ± 1.3%, 2.6 ± 0.9%, and 3.1 ± 1.4% of TPIF, respectively. When comparing \( D_{median} \) between all phases of the study a statis-
tically significant difference was obtained only for MIB vs. BRD \((P = 0.018)\), but not for the mean of BL1 and BL2 vs. MIB or BRD \((P = 0.330\) and \(P = 0.210\), respectively). \(D_t\) did not correlate with the degree of airway obstruction, assessed by z scores of any of the oscillometric measures \((P > 0.6\) for all).

The distribution of the difference between PNT and IP flow signals was slightly dependent on the respiratory phase, illustrated in Fig. 2B. On average, the IP measurement showed a few percentage higher readings than PNT during the 25–50% inspiratory flow range. During expiration the IP readings were higher than PNT at low flows and lower than PNT at high flow rates. However, this behavior was not consistent for all patients. All the deviations from the linearity were rather modest, with the highest single deviation from linearity being \(-15\%\) of TPIF. The most extreme results in Fig. 2B came from three individual patients denoted by letters A, B, and C. Patient A was the child with a history of very low birth weight, BPD and RDS, and highly abnormal lung function at baseline.

In TB parameters the differences between PNT and IP results were \(-0.002 (-0.097 \ldots 0.093), 0.007 (-0.102 \ldots 0.116)\), and \(-0.083 (-0.260 \ldots 0.094)\), respectively for \(T_{PTEF}/T_E\), \(V_{PTEF}/V_E\), and \(S\) presented as mean and 95% confidence interval. The mean differences between PNT and IP as intersubject z-scores were 0.017, 0.066, and 0.82 for \(T_{PTEF}/T_E\), \(V_{PTEF}/V_E\), and \(S\), respectively, showing that the relative difference between PNT and IP was small in \(T_{PTEF}/T_E\) and \(V_{PTEF}/V_E\) but rather large in \(S\). The ICC between PNT and IP were 0.94, 0.91, and 0.68 \((P < 0.0001\) for all), respectively for \(T_{PTEF}/T_E\), \(V_{PTEF}/V_E\), and \(S\). For all parameters the difference was mostly homogeneously distributed as can be observed in the Bland-Altman plot (Fig. 3).

**Tidal breathing parameter changes induced by MIB and BRD.** The 1-min recordings contained 4–26 (median 11.0) acceptable respiratory cycles that were averaged to yield the TB parameter values. The repeatability of TB parameters between baseline measurements 1 and 2 was satisfactory, \(SD_{ws}\) (mean \(\pm\) SD) being 0.047 \(\pm\) 0.049, 0.048 \(\pm\) 0.049, and 0.051 \(\pm\) 0.050 for \(T_{PTEF}/T_E\), \(V_{PTEF}/V_E\), and \(S\), respectively, for PNT and similarly for IP 0.045 \(\pm\) 0.034, 0.053 \(\pm\) 0.041, and 0.062 \(\pm\) 0.041. There was no significant difference between IP and PNT measurements in repeatability as assessed by \(SD_{ws}\) \((P > 0.10\) for all). The absolute values for the TB parameters are presented in Table 2. For \(T_{PTEF}/T_E\), the \(V_{PTEF}/V_E\) parameter value in most patients decreased from baseline to MIB as expected, and increased from MIB to BRD, but there were also individuals for whom this pattern was reversed. In subjects...

---

**Table 2. Values of tidal breathing parameters and oscillometric parameters**

<table>
<thead>
<tr>
<th></th>
<th>BL1 (n = 19)</th>
<th></th>
<th>BL2 (n = 18)</th>
<th></th>
<th>MIB (n = 17)</th>
<th></th>
<th>BRD (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PNT</td>
<td>IP</td>
<td>PNT</td>
<td>IP</td>
<td>PNT</td>
<td>IP</td>
<td>PNT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(T_{PTEF}/T_E)</td>
<td>0.36 ± 0.11</td>
<td>0.36 ± 0.10</td>
<td>0.36 ± 0.12</td>
<td>0.37 ± 0.10</td>
<td>0.31 ± 0.11*</td>
<td>0.31 ± 0.11*</td>
<td>0.35 ± 0.11</td>
</tr>
<tr>
<td>(V_{PTEF}/V_E)</td>
<td>0.36 ± 0.11</td>
<td>0.36 ± 0.09</td>
<td>0.37 ± 0.11</td>
<td>0.38 ± 0.08</td>
<td>0.31 ± 0.10*</td>
<td>0.32 ± 0.09*</td>
<td>0.36 ± 0.10</td>
</tr>
<tr>
<td>(S)</td>
<td>-0.69 ± 0.11</td>
<td>-0.77 ± 0.13</td>
<td>-0.72 ± 0.10</td>
<td>-0.80 ± 0.12</td>
<td>-0.65 ± 0.08</td>
<td>-0.73 ± 0.10</td>
<td>-0.71 ± 0.12</td>
</tr>
<tr>
<td>Oscillometry (n = 21 in all phases)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rs5)</td>
<td>0.82 ± 0.26</td>
<td></td>
<td>1.26 ± 0.31‡</td>
<td></td>
<td>0.71 ± 0.27‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Xs5)</td>
<td>-0.22 ± 0.08</td>
<td></td>
<td>-0.43 ± 0.16½</td>
<td></td>
<td>-0.18 ± 0.07†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Zs5)</td>
<td>0.85 ± 0.27</td>
<td></td>
<td>1.34 ± 0.33‡</td>
<td></td>
<td>0.73 ± 0.27‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means \(\pm SD\), BL1 baseline 1; BL2, baseline 2; MIB, methacholine-induced bronchoconstriction; BRD, bronchodilation; PNT, pneumotachograph; IP, impedance pneumography; \(Rs5\), respiratory resistance at 5 Hz; \(Xs5\), respiratory reactance at 5 Hz; \(Zs5\), total respiratory impedance at 5 Hz. *\(P < 0.05\); †\(P < 0.002\); ‡\(P < 0.00001\) between mean of BL1 and BL2 values and the corresponding value.
with significant MIB assessed by impulse oscillometry, the change in $T_{PTEF}/T_{E}$, $V_{PTEF}/V_{E}$, and $S$ was considered significant (exceeded 1.65 times $SD_{ws}$) in 6, 6, and 5 patients for PNT; and in 6, 6, and 5 patients for IP, respectively.

Table 3 shows the association between MIB- and BRD-induced changes in TB parameters and changes in lung function assessed by impulse oscillometry. The changes in all three TB parameters correlated significantly with the corresponding changes in respiratory resistance and impedance, but only $T_{PTEF}/T_{E}$ and $V_{PTEF}/V_{E}$ correlated with reactance. The association with lung function was evident both in PNT and IP recordings.

**DISCUSSION**

The two compared modes of measurement for tidal flow are based on completely different principles. PNT essentially measures air pressure variations in a tube outside the airway opening, whereas IP measures changes in the electrical conductivity of the thorax. However, the IP with novel filtering technique showed excellent agreement with PNT in the assessment of tidal flow signal in most of the young children we tested. This high agreement was modestly affected by induced bronchoconstriction. The estimated TB parameters and their association with changes in lung function were similar between IP and PNT, thereby showing that IP may be considered as a potential method for recording tidal airflow profiles in young children with wheezing disorders.

Most of our children were too young to perform conventional lung function tests such as spirometry. Therefore, in this experimental design we chose to measure lung function changes by using impulse oscillometry, which enables assessment of mechanical input impedance even in children as young as 2–3 years of age (16). The study group represented young children in need of diagnostic evaluation, and in whom the potential clinical value of IP is highlighted. Because the primary objective was to estimate the agreement of flow signals between the methods and not to test the discriminatory properties of TB parameters measured by IP, healthy subjects were not included in this study.

For assessment of TB, direct measurement of airflow and volume at the airway opening via flow sensors such as PNT is the conventional method (1), and has been successfully applied, i.e., in a prospective cohort studies of infants (11).

Noninvasive respiration measurement methods have been of research interest because they may enable ambulatory long-term assessment of tidal breathing and do not distort the spontaneous breathing pattern as PNT does (8, 23). However, literature on the accuracy of noninvasive measurement methods in respiratory flow assessment is somewhat limited. Jackson et al. (12) found good agreement between respiratory inductance plethysmography (RIP) and PNT for $T_{PTEF}/T_{E}$ in healthy infants and in infants with recurrent wheeze, but concluded that the measurement of $T_{PTEF}/T_{E}$ is not possible with uncalibrated RIP in all infants, particularly at ages beyond the neonatal period and in wheezing subjects. Stick et al. (29) found corresponding agreement in healthy infants. The closest comparative study to ours is that of Manczur et al. (17), who studied RIP in wheezy young children and found agreement with PNT for $T_{PTEF}/T_{E}$ that was slightly less than ours between IP and PNT. They concluded that the mean $T_{PTEF}/T_{E}$ was significantly lower using RIP, and thus results from RIP and PNT are not interchangeable. Having two belts that record chest wall movements, RIP enables an assessment of the degree of thoracoabdominal asynchrony (TAA), but it is questionable how accurately the differentiated sum signal of the belts can represent the air flow at the mouth. Indeed, Jackson et al. discussed that TAA could have been the major contributor to the error in the RIP-derived flow signal. TAA is not as likely a source of error for IP because with appropriately (high) placed electrodes, IP signal reflects lung aeration instead of chest wall movement or the movement of the diaphragm or the liver (13, 15, 19, 24). Two studies have also evaluated the agreement between electromagnetic inductance plethysmography and PNT in infants (33, 19). No previous study has assessed the effect of induced bronchoconstriction on the measurement accuracy or presented flow signal linearity between any noninvasive and direct method in any disease or age group.

**Agreement between measurement methods.** In general, the agreement in flow signal measurement between PNT and IP was excellent both in terms of sample-by-sample absolute signal difference, $D_{SS}$, and PNT-IP flow signal linearity, $D_{L}$ (Fig. 2). Although $D_{SS}$ is small it should not be neglected because it may have some implications for the use of IP. If the measured flow signal is noisy (high $D_{SS}$), more breaths need to be averaged to account for the error caused by the noise.

There was a minor increase in $D_{SS}$ from baseline to MIB and BRD states. Notably, the signal difference between IP and PNT was not related to changes in mechanical impedance measured by the oscillometric technique, suggesting that other mechanisms than changes in airway diameter per se are more important in determining IP accuracy. Increased ventilation heterogeneity induced by methacholine (5) and changes in ventilation/perfusion distribution after inhalation of salbutamol (20) may potentially affect IP measurement. The recorded IP signal is dependent on the volume changes of the lung tissue (19) occurring within the measurement sensitivity region, which is determined by the electrode locations (10). However, such effects were not noticeable in the linearity curve (Fig. 2B). Three individuals showed larger disagreement in linearity between IP and PNT signals. One of them had a history of very low birth weight and bronchopulmonary dysplasia, and highly abnormal lung function with increased ventilation heterogeneity and asynchronous breathing pattern may explain the nonlinear behav-

**Table 3. Correlation between change in tidal breathing parameters and change in oscillometric parameters due to methacholine and bronchodilation**

<table>
<thead>
<tr>
<th></th>
<th>$R_{X_{S_{5}}}$</th>
<th>$X_{R_{X_{S_{5}}}}$</th>
<th>$Z_{R_{X_{S_{5}}}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{PTEF}/T_{E}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNT</td>
<td>$-0.41^{*}$</td>
<td>$-0.49^†$</td>
<td>$-0.44^†$</td>
</tr>
<tr>
<td>IP</td>
<td>$-0.45^†$</td>
<td>$-0.42^†$</td>
<td>$-0.46^†$</td>
</tr>
<tr>
<td>$V_{PTEF}/V_{E}$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNT</td>
<td>$-0.53^‡$</td>
<td>$-0.58^‡$</td>
<td>$-0.55^‡$</td>
</tr>
<tr>
<td>IP</td>
<td>$-0.53^‡$</td>
<td>$-0.45^†$</td>
<td>$-0.54^‡$</td>
</tr>
<tr>
<td>$S$</td>
<td>$0.37^*$</td>
<td>$-0.28$</td>
<td>$0.36^*$</td>
</tr>
<tr>
<td>PNT</td>
<td>$0.40^*$</td>
<td>$-0.32$</td>
<td>$0.39^*$</td>
</tr>
</tbody>
</table>

$R_{X_{S_{5}}}$, respiratory reactance at 5 Hz; $X_{R_{X_{S_{5}}}}$, total respiratory impedance at 5 Hz; $Z_{R_{X_{S_{5}}}}$, pneumotachograph; IP, impedance pneumography. *$P < 0.05$; †$P < 0.02$; ‡$P < 0.005$. 

J Appl Physiol • doi:10.1152/japplphysiol.00657.2013 • www.jappl.org
ior of IP signal. In two subjects, no obvious reasons for higher differences between IP and PNT were found.

The agreement for \( T_{PTEF/T_E} \), the most commonly used TB parameter, was found to be high between PNT and IP and approximately the same as in studies on healthy adults (25) and adults with varying degree of airway obstruction (27). The agreement for \( S \) was lower than those of \( T_{PTEF/T_E} \) and \( V_{PTEF} / V_E \). A potential reason for this is the small residual cardiac distortion left after filtering the IP signal, which may cause large variation in \( S \) as each breath is normalized to the highest encountered value.

**Tidal breathing parameters.** Despite careful controlling of the start of the recording during steady breathing, some of the samples contained episodes of irregular breathing. Understandably, completely relaxed and unattended breathing is difficult to achieve in laboratory conditions in awake young children. However, these problems did not compromise the agreement between IP and PNT signals, or the association of TB parameters with changes in lung function.

We found slightly higher \( T_{PTEF/T_E} \) and \( V_{PTEF} / V_E \) values than Van der Ent et al. (29a) and Cutrera et al. (3), respectively, in a similar study design with children during bronchial challenge. Characteristics of the computer algorithms that derive the parameters may explain the differences with earlier results. The technical and computational aspects of TB recording, for instance—techniques for segmenting the signal into individual exhalations—has been discussed by Bates et al. (1). Van der Ent found a controversial response in \( T_{PTEF/T_E} \) in 5 of 26 patients, which is similar to our findings. Due to complex physiological functions that regulate breathing, measures of TB are influenced by both respiratory mechanics and control of breathing, which may vary individually and temporarily. Although we found significant correlations between lung function assessed by impulse oscillometry and TB parameters, only some of the children showed significant changes (exceeding 1.65 times \( SD_{\text{vs}} \)) in TB parameters during MIB, suggesting that the sensitivity of TB parameters to reflect induced bronchoconstriction is less than that of the oscillometric indices.

Unlike other TB parameters, parameter \( S \) did not change significantly between the phases of the study. However, the association with changes in respiratory resistance and reactance was confirmed in the correlation analyses. In the initial study by Williams et al. (32) of parameter \( S \) on 66 adults, patients were classified into three distinct groups on the basis of visual examination of the expiratory flow curve shape and one of the groups (25% of patients) was left out from the analysis. No such selection was performed in this study, and this likely weakens the statistical significance of our findings.

**Error sources in measurement devices.** The small differences between the PNT and IP flow signals have many potential contributors. The PNT system is reported ambiguously by the manufacturer to have an accuracy of ±5%. As with any instrument, it will have limited linearity. Moreover, the cardiac contraction causes a small volume displacement in the left lung, which is reflected in the PNT flow signal and not known to be accounted for in the PNT system in any way. For IP measurement, the cardiogenic oscillatory distortion is a well-recognized phenomenon that is effectively attenuated by a specialized filtering algorithm (26), but in these short, somewhat irregular segments of tidal breathing the time-adaptive algorithm might not always perform optimally. Furthermore, although care was taken in time-synchronization of IP and PNT signals, it is possible that a small time difference between the signals may contribute to the slight nonlinearity trend observed in Fig. 2B.

**Potential clinical implications.** The major advantage in measuring tidal flow by IP includes minor requirements for cooperation, making the recordings suitable for even young children, undisturbed without PNT. IP also enables measurement of tidal flow in an ambulatory setting (i.e., overnight), offering an interesting tool for studying changes in long-term variations in respiratory mechanics in various research designs. Longer recordings would also increase the statistical power in assessing the TB characteristics, compared with what has been previously possible in laboratory settings, such as in the current study. Further studies are needed to evaluate the clinical usefulness of such applications of IP (e.g., in the management of young children with wheezing disorders).

**Conclusions.** IP and PNT have high agreement in measured respiratory flow signal and derived TB parameters despite induced airway obstruction and irregular breathing in awake young children. MIB induces significant and concurrent changes in TB parameters in most but not all patients, and this can be observed in IP and PNT equally. The results indicate that IP can be considered as a valid method for recording tidal airflow profiles in young children with wheezing disorders.

**GRANTS**

Support for this study was provided by the Tampere Tuberculosis Foundation, the Finnish Funding Agency of Technology and Innovation (Tekes), and the Sigrid Juselius Foundation.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


