Plethysmograph and interrupter resistance measurements in prematurely born young children

Mark R Thomas¹, Gerrard F Rafferty¹, Richard Blowes¹, Janet L Peacock², Neil Marlow³, Sandy Calvert⁴, Anthony Milner¹ & Anne Greenough¹

¹ King’s College
²Brunel University
³University of Nottingham
⁴St George’s Hospital Medical School

Corresponding author:
Anne Greenough
Department of Child Health
4th Floor Golden Jubilee Wing
King’s College Hospital
Bessemer Road
London SE5 9RS

Telephone: 020 7346 3037
Fax: 020 7346 8284
Email: anne.greenough@kcl.ac.uk

Key words: airways resistance, interrupter technique, premature, plethysmography
Abstract

Objective: Airways obstruction in prematurely born young children has frequently been assessed by plethysmographic measurements which require sedation. The interrupter (R\textsubscript{INT}) technique does not require sedation, but has rarely been examined in children under two years of age. Our aim was to compare R\textsubscript{INT} results to those of plethysmographic measurements of airway resistance in prematurely born, young children.

Design: Prospective study.

Setting: Infant and paediatric lung function laboratories.

Patients: Thirty children with a median gestational age of 25-29 weeks, and median postnatal age of 13 months.

Interventions and main outcome measures: The infants were sedated, airway resistance was measured by total body plethysmography (Raw) and R\textsubscript{INT} measurements were made using a MicroR\textsubscript{INT} device. Further Raw and R\textsubscript{INT} measurements were made after salbutamol administration, if the children remained asleep.

Results: Baseline measurements of Raw and R\textsubscript{INT} were obtained from 30 and 26 (respectively) of the children. The baseline mean R\textsubscript{INT} values were higher than the baseline mean Raw results (3.45 vs 2.84kPa/[l/s], p = 0.006), limits of agreement for mean (R\textsubscript{INT} - Raw) -1.52 to 2.74 kPa(l/sec). Ten infants received salbutamol, after which their mean R\textsubscript{INT} result was 3.6 kPa/[l/s] and mean Raw was 3.1 kPa/[l/s], limits of agreement -0.28 to 1.44 kPa(l/sec).

Conclusion: The poor agreement we note between R\textsubscript{INT} and Raw results suggest that R\textsubscript{INT} measurements cannot substitute for plethysmographic measurements in sedated prematurely born infants.
Introduction

Prematurely born infants frequently have troublesome wheeze at follow up, particularly in the first two years after birth. It is, therefore, important to assess the degree of airways obstruction in such children, as a consequence plethysmographic measurement of airways resistance has been undertaken.[1][2] In addition, many interventions are undertaken in the neonatal period with the hope of improving pulmonary outcome; plethysmographic measurements have been made to provide an objective assessment of the effect of the interventions.[3] Unfortunately very young children must be sedated to undergo plethysmographic measurements and this limits their acceptability to parents, resulting in loss to follow up.[3] It is, therefore, important to identify a measurement of airways obstruction in prematurely born young children that does not require sedation and yields reliable information. A possibility is the interrupter technique (R_INT), which has been used to assess airways obstruction in older children [4][5][6][7], many studies have concentrated on its possible research and clinical role in preschool children.[8][9][10][11][12][13][14][15][16][17][18][19] There are, however, limited data from children of less than two years. In such an age group, studied outside the first few months of birth comparison of R_INT results with standard techniques requires assessment in a sedated population. Comparison of results using the R_INT technique have been made to those of measurements of single breath lung mechanics and the forced expiratory flow volume technique in sedated infants, all less than 18 months of age.[20] Satisfactory R_INT measurements could only be made in 25 of the 37 infants, but in those infants significant correlations between the results using the R_INT and both single breath resistance measurements and maximum flow at functional residual capacity (correlations of 0.7 and 0.63 respectively) were demonstrated.[20] Although comparisons of the results of R_INT measurements have been made to those of plethysmographic airway measurements in school age children [4] there are no similar comparisons in very young children.[21] The aim of this study, therefore, was to compare R_INT measurement results to those of airway resistance measured by total body plethysmography (Raw) in very prematurely born children less than two years of age.

Materials and Methods

Study subjects

Children who were attending for pulmonary function follow up at one year corrected as part of the United Kingdom Oscillation Study (UKOS) (prophylactic high frequency oscillatory ventilation versus conventional ventilation in very preterm infants) [22] were recruited into this study. The study was approved by the King’s College Hospital Ethics Committee and parents gave informed written consent for their child to take part. All of the infants entered into the UKOS trial were born at less than 29 weeks of gestation. Measurements were attempted on 30 children with a median gestational age of 25.9 (range 23 –28.9) weeks and a median corrected postnatal age of 13 (range 11-14) months.

Study design

The children were seen in the Infant and Paediatric Respiratory Lung Function Laboratories. A history was taken and the children were examined. No child was measured within two
weeks of a respiratory infection, and, only if no respiratory abnormalities indicating acute infection were found on examination, were the children sedated with chloral hydrate syrup (80mg/kg). Those not asleep within 30 minutes received an additional 40mg/kg of chloral hydrate. Once asleep, measurements of Raw and then $R_{INT}$ were made. Children who remained sedated after the baseline measurements were given salbutamol (200 micrograms) via a spacer device and face mask (Volumatic, Allen & Hanbury), further Raw then $R_{INT}$ measurements were then made. The $R_{INT}$ measurements were always made after the measurement of Raw, as the Raw data collection was essential for a larger study.[3]

Methods

The child was placed within a 90 litre total body plethysmograph (Department of Medical Engineering, Hammersmith Hospital, London) and a Rendell-Baker face mask lowered onto their face. A rim of silicone putty was used to obtain an airtight seal around the nose and mouth. The rim of the facemask supported the cheeks during the measurements. Details of the plethysmograph and calibration techniques are given elsewhere.[23] The plethysmograph was sealed and functional residual capacity ($FRC_{pleth}$) measured from a minimum of three end-inspiratory occlusions. Raw was then determined from a minimum of five technically acceptable breaths. The median number of breaths per child analysed pre and post bronchodilator were 9.5 and 10 respectively. The $FRC_{pleth}$ and Raw measurements were calculated using software developed for the laboratory. Raw results were obtained from a best fit regression line drawn through the first 50% of the inspiratory flow/plethysmograph pressure trace.[23] Only breaths in which the loop was closed or nearly closed at points of zero flow were used for the analysis.[23] The plethysmograph was then opened and $R_{INT}$ measured with the $R_{INT}$ device (Micro$R_{INT}$, Micromedical Ltd, Rochester, Kent, UK). The $R_{INT}$ device was set to trigger at peak inspiratory flow. The $R_{INT}$ values were calculated automatically by the device. The pressure plateau was regressed back to the time of occlusion from pressure measurements 30 and 70 milliseconds after the occlusion. The flow used was that immediately before the occlusion. If there was an obvious leak or the pressure trace after the immediate oscillations was not linear [18], the occlusion was deemed unsatisfactory and discarded. The $R_{INT}$ device makes 10 occlusions in succession for each test. Only the results from children in whom at least five satisfactory occlusions were made were included in the analysis. If there were less than five satisfactory occlusions from the first set of measurements then a further set of occlusions was repeated. The median number of occlusions per child analysed pre-bronchodilator and post-bronchodilator was 7.5 and 9.0 respectively.

Analysis

For each child the mean and standard deviation (SD) Raw and $R_{INT}$ values were calculated from the respective repeated measures and the within infant coefficient of variation (CV) thus derived (100% xSD/mean). Raw and $R_{INT}$ data were both approximately normally distributed, but $R_{INT}$ data had a very slight skew, which was not corrected by transformation and so analyses based on normal distribution were used. Coefficients of variation were calculated for Raw and $R_{INT}$ to assess within individual reliability. The within child difference between the $R_{INT}$ and Raw values was tested for significance using the t-test. The agreement between the Raw and $R_{INT}$ measurements was estimated using the Bland-Altman limits of agreement method.[24] The limits of agreement were calculated using mean difference ± t x SD, where t is the 5% point of the t distribution. These provide an estimate of the minimum and maximum likely difference between the two measurements and thus
provide quantitative information on the extent of the agreement. Pearson’s correlation coefficients were also calculated to allow comparison with data from a paper evaluating the interrupter technique in comparison to plethysmographic assessment of airway resistance in children.[4]

**Results**

Satisfactory Raw and R\textsubscript{INT} baseline measurements were obtained in 26 of 30 children (table) (Figure 1). Technically acceptable loops for Raw measurements were obtained in all 30 children. Four children had fewer than five satisfactory R\textsubscript{INT} results, all four children waking up during the measurements. The R\textsubscript{INT} values tended to be higher than the Raw values (mean R\textsubscript{INT} 3.45 (SD 1.29) kPa/[l/s] mean Raw 2.84 (SD 0.80) kPa/[l/s]), (p = 0.006). The mean CVs were 12.4% for R\textsubscript{INT} and 12.6% for Raw baseline results. Following the baseline measurements, ten children remained asleep and were restudied after bronchodilator administration. This subgroup had mean baseline R\textsubscript{INT} and Raw results of 3.75 (SD 1.46) kPa/[l/sec] and 3.17 (SD 0.95) kPa/[l/s] respectively. After salbutamol administration, the respective mean R\textsubscript{INT} and Raw results were 3.63 (SD 1.30) kPa and 3.05 (SD 1.14) kPa [l/s]. Neither the change in Raw nor R\textsubscript{INT} following bronchodilator administration were significant.

The mean difference (SD) between R\textsubscript{INT} and Raw (R\textsubscript{INT} -Raw) results in children with satisfactory baseline measurements was 0.61 (1.03) giving limits of agreement of –1.53 to 2.74 kPa (l/sec) (fig 1). For those children who received salbutamol the mean difference (SD) between the R\textsubscript{INT} and Raw results after salbutamol administration was slightly smaller with less variability between subjects being 0.58 (0.38) giving narrower limits of agreement of –0.28 to 1.44 kPa(l/sec) (Figure 3). The correlation coefficients of Raw and R\textsubscript{INT} results were 0.60 in the 26 children with paired measurements prior to bronchodilator and 0.96 in the ten children who had paired measurements post bronchodilator.

Table: Comparison of the characteristics of the R\textsubscript{INT} and Raw results of the study population, those with satisfactory R\textsubscript{INT} results and those measured after salbutamol administration

<table>
<thead>
<tr>
<th></th>
<th>Study Population</th>
<th>Children with Satisfactory R\textsubscript{INT} results</th>
<th>Children measured after Salbutamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>30</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>25.9 (1.6)</td>
<td>26.0 (1.6)</td>
<td>25.5 (1.3)</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>814 (205)</td>
<td>836 (212)</td>
<td>768 (152)</td>
</tr>
<tr>
<td>At the time of testing:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>corrected age (months)</td>
<td>12.8 (1.1)</td>
<td>12.8 (1.1)</td>
<td>13.0 (0.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>8.9 (1.3)</td>
<td>9.0 (1.2)</td>
<td>9.0 (1.2)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>74.5 (3.2)</td>
<td>74.9 (2.9)</td>
<td>74.9 (3.7)</td>
</tr>
<tr>
<td>Pre bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRC\textsubscript{pleth} (ml/kg)</td>
<td>26.1 (5.9)</td>
<td>26.1 (5.9)</td>
<td>23.9 (4.1)</td>
</tr>
<tr>
<td>Raw (kPa/[l/s])</td>
<td>3.01 (1.01)</td>
<td>2.84 (0.80)</td>
<td>3.17 (0.95)</td>
</tr>
<tr>
<td>R\textsubscript{INT} (kPa/[l/s])</td>
<td>-</td>
<td>3.45 (1.29)</td>
<td>3.75 (1.46)</td>
</tr>
<tr>
<td>Post-bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raw (kPa/[l/s])</td>
<td>-</td>
<td>-</td>
<td>3.05 (1.14)</td>
</tr>
<tr>
<td>R\textsubscript{INT} (kPa/[l/s])</td>
<td>-</td>
<td>-</td>
<td>3.63 (1.30)</td>
</tr>
</tbody>
</table>
Discussion

We have demonstrated poor agreement between R\textsubscript{INT} and Raw results in sedated very prematurely born, young children. Very prematurely born children were chosen as the population, as such children are frequently symptomatic at follow up and require respiratory function assessment. In addition, we expected them to have a wide range of resistance values and thus in such a population we could make an extensive comparison of R\textsubscript{INT} and Raw results. (Figure 1) The correlation coefficient we report post bronchodilator was similar to that reported in children when R\textsubscript{INT} results were compared to airway resistance results obtained by plethysmography (r=0.91). Such high correlations, however, are not unexpected, as the techniques are assessing related aspects of lung function and correlations then do not inform the level of agreement. The more appropriate method to determine if the results of two techniques are in agreement is Bland and Altman analysis.[24] Using that analysis, we demonstrated poor agreement between the two techniques.

It was possible to obtain at least five satisfactory R\textsubscript{INT} baseline results in 26 of the 30 young children. The children in whom five acceptable R\textsubscript{INT} results were not obtained, all woke from their sedation during the measurement sequence. In all the children who remained asleep, five acceptable R\textsubscript{INT} results were obtained, thus, our results confirm that the R\textsubscript{INT} technique is easy to use in sedated patients.[20]

The baseline R\textsubscript{INT} values were on average 0.61 Kpa/sec higher than the Raw results, as has been found in school aged children.[4] An explanation for this difference is that R\textsubscript{INT} measurements are claimed to also include a component from the chest wall and possibly a lung tissue component.[4] A further explanation for the difference in the R\textsubscript{INT} and Raw results in the present study was that R\textsubscript{INT} results were made at peak inspiratory flow, whereas Raw measurement results were calculated from the best fit up to 50% of peak flow. At peak inspiratory flow, flow is more likely to be turbulent than laminar resulting in higher resistance values. We deliberately chose to make inspiratory interruptions as we wished to compare the results of the R\textsubscript{INT} technique to those made by plethysmographic measurements. Inspiratory rather than expiratory airway resistance has most usually been assessed by plethysmography, when that technique has been used to determine the respiratory function of very young children.

We report the first comparison of the reproducibility of these two techniques in children younger than two years of age. The reproducibility of the techniques was not calculated by obtaining mean values before and after replacing the facemask or before and after the child had been taken out of the plethysmograph, as the extra time such a protocol would have taken would have precluded studying the children before and after salbutamol administration. The reproducibility of the measurements was determined by calculating a coefficient of variation for each measurement (a minimum of five on each occasion). We calculated such coefficients of variation for both techniques allowing us to compare their reproducibility techniques and we found the two techniques to have similar reproducibility. However, measurements during expiration may be more sensitive in detecting pathological airway patency.

For logistical reasons, we did not randomise the order of measurement technique and it is possible that the sleep stage of the infants varied during the course of each study affecting the reproducibility of the techniques. We do not, however, feel that variation in the sleep state of the children influenced the R\textsubscript{INT} and Raw results. Although it has been suggested that sleep
state affected lung volume [25] and hence might affect $R_{\text{INT}}$ and Raw, subsequent studies demonstrated sleep stage had no affect on lung volume.[26][27] It is of interest that the results of the two techniques differed less when the measurements were made after rather than before bronchodilator administration, that is in the population of infants who had remained longer asleep. Nevertheless, $R_{\text{INT}}$ and Raw results differed significantly even in those infants who were measured post bronchodilator and asleep longest.

In conclusion, these results demonstrate that the $R_{\text{INT}}$ technique is easy to use in sedated infants. There was, however, poor agreement between $R_{\text{INT}}$ and Raw results in very prematurely born infants when studied sedated. $R_{\text{INT}}$ results are influenced by the method of measuring pressures from the recording. The device we used determines the pressure by back-regression from 70 to 30 milliseconds, there are, however, other ways of determining the pressure.[18][19] It is, therefore, important to emphasize that our results pertain to a particular method of measuring $R_{\text{INT}}$ and the plethysmographic technique we used to assess airways obstruction. Our results demonstrate that $R_{\text{INT}}$ measured by the Micro$R_{\text{INT}}$ method cannot substitute for plethysmographic measurements of airway resistance.
Acknowledgements
Dr Thomas and the UKOS Study were supported by the Medical Research Council.

Competing Interests
None

Licence Statement
The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Archives of Disease in Childhood, editions and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://adc.bmjjournals.com/misc/ifora/licencform.shtml).

Figure Legends

**Figure 1**
Plot of $R_{INT}$ and Raw values from the 26 infants in whom both $R_{INT}$ and Raw values were successfully obtained prior to bronchodilator.

**Figure 2**
Bland and Altman plot demonstrating the mean difference and limits of agreement of the $R_{INT}$ and Raw results pre-bronchodilator (n=26). Limits of agreement are $0.61 \pm 2.06 \times 1.03$ where 2.06 is two sided 5% point for t distribution with 25 degrees of freedom

**Figure 3**
Bland and Altman plot demonstrating the mean difference and limits of agreement of the $R_{INT}$ and Raw results post-bronchodilator (n=10). Limits of agreement are $0.58 \pm 2.26 \times 0.38$ where 2.26 is two sided 5% point for t distribution with nine degrees of freedom

What is already known on this topic
Prematurely born young children frequently have troublesome wheeze at follow up. The interrupter technique ($R_{INT}$) assesses airway obstruction and is potentially attractive as it can be performed without sedation. No comparisons, however, have been made of the results of $R_{INT}$ measurements to those of plethysmographic airway resistance measurements, a standard method of assessing airway obstruction in prematurely born young children.

What this study adds
Poor limits of agreement of the results of the two techniques were demonstrated in sedated prematurely born young children suggesting that $R_{INT}$ measurements using the micro$R_{INT}$ technique cannot substitute for plethysmographic measurements of airway resistance in sedated, prematurely born children.
References


