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Evaluation of a new interrupter device for measuring bronchial responsiveness and the response to bronchodilator in 3 year old children

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ABSTRACT: The interrupter technique for measuring airway resistance is noninvasive and convenient, and therefore ideally suited for the assessment of induced changes in airway calibre in preschool children. The aim of this study was to evaluate a commercially available interrupter device (based on Microlab 4000), which calculates the interrupter resistance (R_{int}) from pressure and flow following a brief interruption of expiration during quiet breathing.

The repeatability of R_{int} was assessed, and its response to methacholine challenge and the bronchodilator salbutamol were compared with an indirect technique, the fall in transcutaneous oxygen tension (P_{tc,O_2}), using the sensitivity index (SI, *i.e.* the change after challenge expressed in multiples of the baseline standard deviation) in 12 wheezy children (aged 3 yrs±2 months).

The mean (SD) baseline value of R_{int} was 0.91 (0.20) kPa·L^{-1}·s. Short-term repeatability and baseline variability were satisfactory for R_{int} (intraclass correlation coefficient = 0.6; mean intrasubject coefficient of variation = 13%). Although 10 of the 12 subjects obtained a significant response using R_{int} at maximal bronchoconstriction (*i.e.* SI >2), overall, R_{int} was five times less sensitive than P_{tc,O_2} (geometric mean SI: R_{int} 3 vs P_{tc,O_2} 16; p<0.0001). Reversal of obstruction with administration of a bronchodilator was clearly demonstrated in almost all subjects: R_{int} after challenge (mean±SD) 1.25 (0.22) kPa·L^{-1}·s; after salbutamol 0.78 (0.19) kPa·L^{-1}·s; p<0.001.

In conclusion, the convenient interrupter resistance method appears more promising for detecting bronchodilator responses than induced bronchoconstriction in wheezy preschool children; however, measurement of transcutaneous oxygen tension provides a reliable indirect means of detecting induced airway obstruction in this age-group.

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Very few reliable techniques are available to assess lung function in the young child. As a result, measurement of airway responsiveness in the growing child remains incomplete. The fall in transcutaneous oxygen tension (P_{tc,O_2}) has proved to be a reliable, robust method for the measurement of the response to bronchial challenge [1–5], although it is an indirect measure of change in airway calibre, thought to result from increased ventilation-perfusion mismatch [6]. An alteration in breath sounds upon auscultation of the chest has been reported as a measure of response [7, 8], but lacks sensitivity [9]. The forced oscillation technique (FOT), although recommended for preschool children [10, 11], has been demonstrated to be less reliable than originally thought after induced bronchoconstriction [9, 12].

The interrupter technique, like forced oscillation, is a noninvasive method of measuring airway resistance and makes few demands on the subject; it is, therefore, ideally suited to this age-group. The technique assumes that immediately following a brief interruption of airflow, alveolar pressure (P_{alv}) will rapidly equilibrate with pressure at the mouth (P_{mo}) [13]. The resistance of the airways can then be estimated by calculating the ratio of the pressure change at the mouth to flow at the time of occlusion [14, 15]. In previous studies, we validated the measurement of interrupter resistance (R_{int}) for detecting a response to inhaled methacholine in 5 year old asthmatic children and in normal adults [12, 16, 17]. R_{int} was found to be similar in sensitivity to the FOT in 5 year olds [12]. Although less sensitive when compared to airway resistance (R_{aw}) measured plethysmographically, or total lung resistance using an oesophageal balloon [17], R_{int} was capable of detecting significant increases in resistance in adults. It has also been reported that R_{int} is equally as sensitive as R_{aw} in detecting the airway response to bronchodilator therapy in older children and adults [18, 19], whilst others have applied the technique to infants [20] and the growing child [21].

The aim of the present study was to provide an evaluation of the interrupter technique in a group of 3 year old asthmatic children, using a new, commercially available, handheld interrupter device [19]. Using the device, the interrupter resistance of each breathing cycle could be recorded, thus permitting the construction of concentration-response curves after inducing airway obstruction by methacholine challenge. For comparison, measurements of transcutaneous oxygen tension, previously found acceptable in this age-group, were made. Reversal of obstruction with a β-agonist bronchodilator at the end of the challenge was used to evaluate the potential of the technique for detecting improvement in airway calibre.

Methods

Subjects

Twelve children with episodic or persistent wheeze, all within 2 months of their third birthday (9 boys and 3 girls) were recruited from an ongoing cohort being studied in the Paediatric Out-patient Department. Bronchodilator and cromoglycate therapy were withheld for at least 12 h before each study, but topical corticosteroids were taken as usual. Approval was obtained from the Hospital Ethics Committee and parents gave their written consent.

Methacholine challenge

The challenge test was carried out using a continuous inhalation, tidal breathing method. This method was chosen because the test required only minimal subject co-operation and could, therefore, be applied to young children. Aerosols of methacholine chloride (Sigma Chemicals Ltd, Poole, Dorset, UK) were delivered from a Wright nebulizer producing an output of 0.14 $mL \cdot min^{-1}$ (SD ±0.01 $mL \cdot min^{-1}$) using 8 $L \cdot min^{-1}$ of air as the driving gas.

A clip was placed on the nose and the methacholine aerosol was inhaled through a mouthpiece during quiet breathing for 1 min. Methacholine was inhaled at 5 min intervals, firstly in fourfold increasing concentrations from 0.5 $mg \cdot mL^{-1}$, and then in twofold increasing concentrations after the P_{tc,O_2} had fallen by approximately 1 kPa (about 10%) from the mean baseline value. The challenge was performed using initially large concentration steps of methacholine in order to shorten the duration of the test [2]. The challenge was continued until a 20% fall in P_{tc,O_2} had occurred or the maximum concentration of 16 $mg \cdot mL^{-1}$ had been delivered, whichever occurred soonest. Airway obstruction was relieved at the end of the challenge by nebulized salbutamol (2.5 mg) given *via* a face mask.

Measurement of response to challenge

Interrupter resistance. The interrupter device (prototype of Microlab 4000; Micro Medical Ltd, Rochester, Kent, UK) consisted of an interrupting valve and transducer unit connected to a customized, miniature computer [19]. The head of the transducer unit allowed connection to a face mask. The interrupter valve closed in about 5 ms. A screen pneumotachograph placed between the pressure sensor and the interrupter valve was used to measure flow. The unit was calibrated for measurement of pressure by connecting the transducer head directly to a manometer. Flow calibration was achieved by passing a reference flow through the transducer head *via* a certified flowmeter (Rotameter, Fisher Controls, Croydon, UK). The microcomputer provided instantaneous calculation of results, which could be printed for inspection after each interruption.

The interrupter device could be programmed to interrupt the airflow during tidal expiration at a predetermined flow. A flow rate of 0.2 $L \cdot s^{-1}$ was chosen. This corresponded to near maximal tidal expiratory flow in this age-group and produced an optimal $P_{mo(t)}$ signal. The valve was then held in the closed position for 100 ms, whilst pressure values were recorded at 1 ms intervals and stored in memory. The valve then reopened and the pressure data were used to calculate R_{int} automatically. The interruption P_{mo} signal consists of a rapid initial phase followed by a slower secondary phase separated by high frequency oscillations [14] (fig. 1). The algorithm used to calculate R_{int} from the secondary pressure phase involves a simple, two-point linear regression of the postocclusion signal, which is back-extrapolated to an arbitrary time after valve closure. The time of complete valve closure (t) is taken as occurring at 25% of the peak value of the first oscillation upstroke [19]. The points are based on the mean pressure values for two 10 ms portions of the data centred on t+30 ms (range t+25 to t+35 ms) and t+70 ms (range t+65 to t+75 ms) which are then linearly back-extrapolated to 15 ms after the valve closure time (*i.e.*. t+15 ms). The difference between this calculated pressure (P_{int}) and the preocclusion mouth pressure (P_{pre}) (due to apparatus resistance) is then divided by the preprogrammed value of flow to give the interrupter resistance.

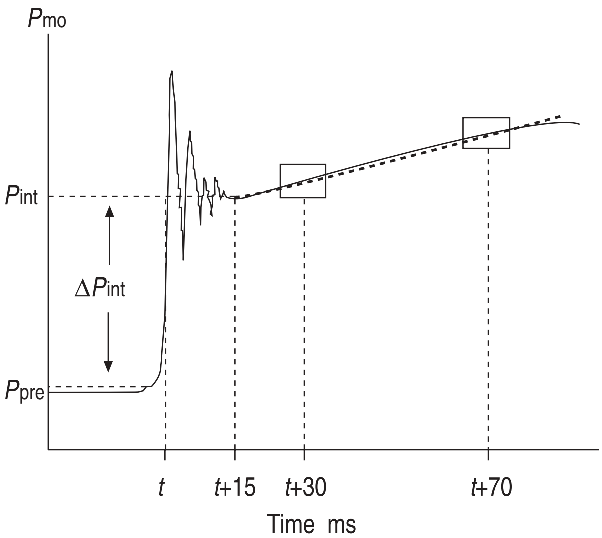

Fig. 1. – Schematic diagram illustrating the calculation of interrupter pressure. The moment of valve closure (t) was taken as the point at which 25% of the first pressure upstroke had been reached. The mean pressure values for two 10 ms portions of the data centred on times t +30ms and t +70 ms were linearly back-extrapolated to 15 ms after the valve closure time (*i.e.* t + 15 ms) to provide the interruption pressure, (P_{int}). The interruption pressure change was calculated as the difference between P_{int} and the preocclusion pressure, (P_{pre}). P_{mo}: mouth pressure.

During the measurement of R_{int}, the child breathed through a transparent paediatric oronasal face mask with an inflatable air cushion seal. The children were instructed to keep their mouths open but it was not possible to determine whether they were nose or mouth breathing. A series of "practice" attempts were made so that the child could get accustomed to the equipment and the "clicking" noises as the valve closed and reopened. The child's head was supported by the operator and the mask was firmly applied to prevent leakage, as confirmed by inspection of the $P_{mo(t)}$ waveform (see below). Interrupter measurements were made at the same flow and at the same point on each consecutive breathing cycle.

Data were rejected according to the following criteria: if there was any drift in the baseline; if the extrapolated pressure value was unusually small, indicating mask leakage; or extremely high, indicating either glottic closure, irregular breathing or respiratory muscle activity. Initial readings of R_{int} (which included baseline and the extrapolated mouth pressure) were printed with the $P_{mo(t)}$ curve for inspection; these could be compared with the values without a print-out of the $P_{mo(t)}$ curves when using the device in continuous operation, which further aided the identification of abnormal data. It was not possible to print out every $P_{mo(t)}$ curve because of time restrictions after inhaling methacholine.

In order to test the repeatability of R_{int}, three sets of six baseline measurements ($R1$, $R2$ and $R3$) were taken with a l5 s interval between each set. Six measurements were taken after methacholine and bronchodilator administration. The value of R_{int} is given as the mean of the six recordings whenever measured.

Transcutaneous oxygen tension. P_{tc,O_2} was measured with a skin electrode (Cutan P_{O_2} monitor 820, Kontron Instruments, Switzerland) attached to the chest wall and heated to 44°C [1]. The electrode was calibrated before use in air (20.9 kPa). After at least a 20 min equilibration period to allow the P_{tc,O_2} to stabilize, baseline values were obtained manually at 1 min intervals for 8 min. P_{tc,O_2} values were recorded at precisely 1 min intervals for 3 min after the end of each nebulization. During measurements, the subject was encouraged to remain as quiet as possible. Coughing, taking big breaths, or vigorous movement may have altered the blood gas readings. The fall in P_{tc,O_2} occurring 3 min after each inhalation was used to construct a concentration-response curve.

Expression of results and statistical analysis

Repeatability of baseline P_{tc,O_2} was assessed using the within-subject coefficient of variation (CoV), the standard deviation of repeat measurements expressed as a percentage of the mean. The repeatability of consecutive sets of R_{int} baselines was calculated using the intraclass correlation (IC) coefficient, a dimensionless measure of repeatability, by dividing the between subject variance by the variance in a one-way analysis of variance (ANOVA) [22]. Measurement sensitivity was expressed as the percentage change from baseline after bronchoconstriction and as a sensitivity index (SI), *i.e.* the absolute change after challenge in multiples of the baseline standard deviation as described by BUHR *et al.* [11]. Baseline values and postchallenge or postbronchodilator measurements were compared by paired t-test. Log transformed SI values and percentage changes were analysed using ANOVA and paired t-tests.

Results

Baseline measurements

All subjects readily accepted the face mask, adapted quickly to the clicking noises of the valve after a short "practice", and settled down to breathe quietly. Children were not distressed, even after maximally induced bronchoconsriction, while breathing through the interrupter valve. The baseline variability of repeated sets of R_{int} measurements ($R1$–$R3$) is indicated in table 1. The intraclass correlation (IC=0.6) indicated a satisfactory level

Table 1. – Repeatability of baseline interrupter resistance and comparison of variability of R_{int} and P_{tc,O_2} for each 3 year old subject

Subject No.	R_{int} Baseline values kPa·L^{-1}·s $R1$*	$R2$*	$R3$*	CoV$^+$ %	P_{tc,O_2} CoV$^\#$ %
1	1.20±0.12	1.4±0.13	1.20±0.05	8.7	0.7
2	0.55±0.20	0.47±0.20	0.52±0.14	35.3	3.2
3	1.00±0.06	0.84±0.05	0.95±0.16	10.8	2.4
4	1.10±0.09	1.01±0.15	1.09±0.09	10.4	0.4
5	0.76±0.18	0.77±0.13	0.74±0.16	21.1	1.6
6	1.19±0.05	1.13±0.05	1.10±0.05	4.4	1.3
7	0.85±0.11	0.93±0.07	0.91±0.11	11.2	0.9
8	0.87±0.04	1.03±0.05	1.08±0.09	6.1	0.8
9	1.04±0.09	0.88±0.05	0.75±0.10	8.9	1.6
10	1.02±0.08	0.90±0.15	0.89±0.05	10.6	2.2
11	0.83±0.04	0.69±0.08	0.66±0.20	16.7	1.9
12	0.82±0.08	0.75±0.10	0.73±0.12	13.0	1.8
Mean	0.94	0.90	0.89	13.1	1.6

$^+$: CoV based on pooled estimate of 18 measurements; $^\#$: CoV based on pooled estimate of 8 measurements; *: each value is the mean±1SD R_{int} of six consecutive measurements. R_{int}: interrupter resistance; P_{tc,O_2}: transcutaneous oxygen tension; CoV: coefficient of variation.

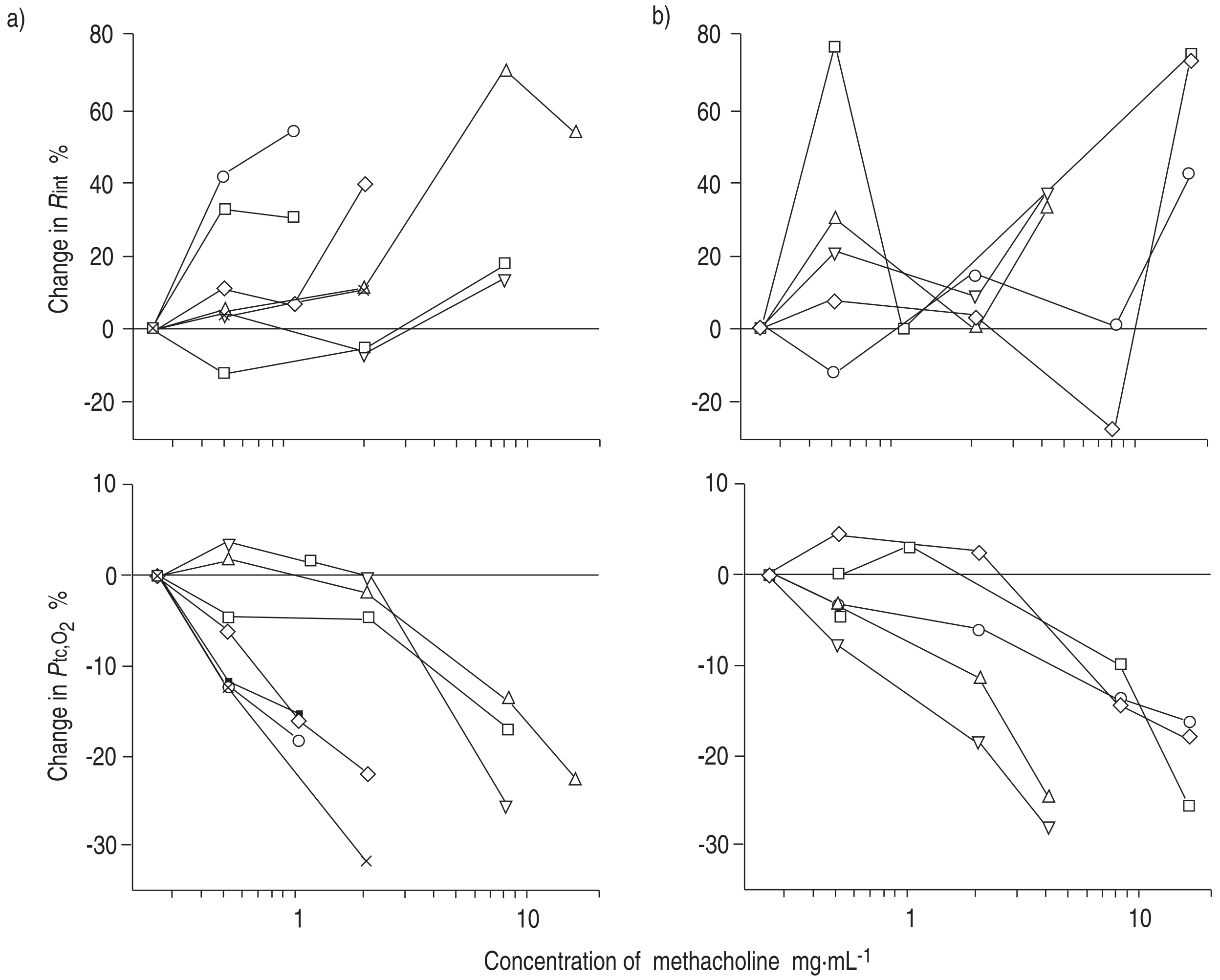

Fig. 2. – Comparison of changes in interrupter resistance (*R*int) and transcutaneous oxygen pressure (P_{tc,O_2}) in 12 children aged 3 yrs: a) subjects showing a consistent increase in *R*int with increasing concentration of inhaled methacholine; b) subjects with inconsistent changes in *R*int with increasing concentration of inhaled methacholine.

of measurement repeatability. The mean within subject CoV based on the pooled estimate of all baseline measurements (total of 18 measurements) ranged 4–35%, with a mean of 13% (table 1). In contrast, the mean CoV for P_{tc,O_2} measurements (based on eight observations) was 10 fold smaller (range 0.4–3.2%, mean 1.6%).

Comparison of concentration response curves for Rint *and* P_{tc,O_2}

In contrast to the consistent concentration-response relationships for all subjects using P_{tc,O_2}, those for *R*int were inconsistent in five subjects (fig. 2). For the group as a whole, a significant change ($p<0.0001$) in both *R*int and P_{tc,O_2} was obtained at maximal bronchoconstriction.

Sensitivity of Rint *to detect change in airway calibre during methacholine challenge and following bronchodilation*

Following a ≥15% change in P_{tc,O_2} in all subjects after the maximum concentration of methacholine administered, a change in *R*int of ≥30% or ≥40% was obtained in 9 and 6 out of 12 subjects, respectively (table 2). The geometric mean SI value for *R*int was about five times smaller ($p<0.0001$) than that obtained for P_{tc,O_2}.

Following bronchodilator, the fall in *R*int was significant (*i.e.* >2 SD fall in *R*int from mean post-challenge value) in 11 of the 12 subjects (fig. 3, table 2). In the remaining subject (No. 12), the fall in *R*int after bronchodilator was comparable in magnitude to the rise in *R*int induced in the challenge; however, these changes were not significant. The geometric mean SI for the reversal in bronchoconstriction using *R*int was 4.9.

Discussion

In this study, an evaluation of a new hand held interrupter device for assessing the response to changes in airway calibre was performed in 3 year old children. We found that in several subjects it was impossible to detect significant responses to bronchoprovocation despite a clear change in P_{tc,O_2}. However, the interrupter device could be used to detect a reversal in obstruction after administration of salbutamol in almost all subjects, perhaps because the absolute change in resistance was

Table 2. – Comparison of response to methacholine challenge measured using R_{int} and P_{tc,O_2} and after reversal of obstruction with salbutamol measured in 12 children aged 3 yrs

Subject No.	P_{tc,O_2} Baseline Mean kPa	P_{tc,O_2} Max bronchoconstriction Mean kPa	Change %	SI	R_{int} Baseline Mean+ kPa·L^{-1}·s	R_{int} Max bronchoconstriction Mean kPa·L^{-1}·s	Change %	SI	Postsalbutamol Mean kPa·L^{-1}·s	Change* %	SI
1	11.3	9.6	-15	21.3	1.26	1.65	31	3.6	0.96	-72	8.3
2	10.3	7.7	-25	7.7	0.51	0.89	75	2.1	0.50	-78	2.2
3	9.9	8.1	-18	7.5	0.93	1.43	54	5.0	0.91	-57	5.3
4	11.4	8.6	-25	7.0	1.06	1.41	33	3.2	0.53	-166	16.0
5	11.1	8.6	-23	13.9	0.76	1.17	54	2.6	0.55	-113	5.3
6	10.7	8.0	-25	30.0	1.14	1.30	14	3.2	1.00	-30	6.8
7	11.9	10.0	-16	17.3	0.89	1.26	42	3.8	0.89	-42	3.7
8	10.1	7.9	-22	27.5	0.99	1.39	40	6.6	1.00	-39	6.4
9	8.9	6.4	-28	17.9	0.90	1.23	37	4.2	0.90	-37	4.1
10	11.4	7.8	-32	14.4	0.94	1.04	11	1.0	0.81	-28	2.7
11	12.0	9.9	-18	9.1	0.73	1.26	73	4.4	0.58	-117	7.0
12	8.9	7.4	-17	9.4	0.77	0.91	18	1.4	0.75	-21	1.6
Mean	10.7	8.3	-22	16.4#	0.91	1.25	40	3.0#	0.78	67	4.9#

*: calculated as percentage change from maximum bronchoconstriction value; +: based on pooled estimate of 18 measurements; #: geometric mean. P_{tc,O_2}: transcutaneous oxygen tension; R_{int}: interrupter resistance; SI: sensitivity index.

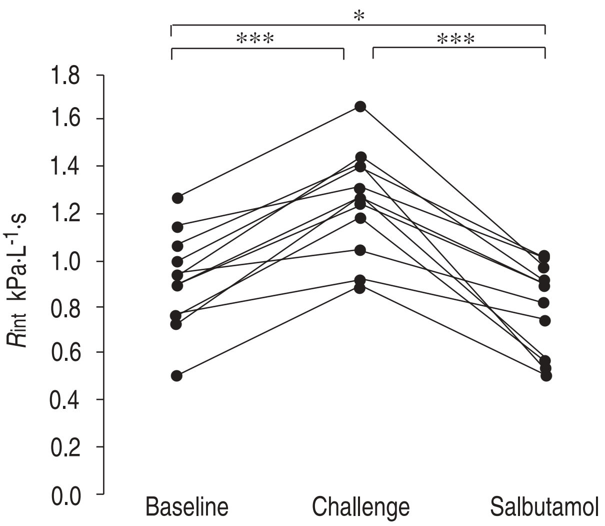

Fig. 3. – Individual values of baseline interrupter resistance, after maximal methacholine-induced bronchoconstriction and 15 min following reversal with administration of salbutamol in 12 children aged 3 yrs. *: p<0.05; ***: p<0.0001.

greater after bronchodilator, or due to an improvement in the estimation of alveolar pressure itself.

In order to determine the baseline variability of R_{int}, we measured three consecutive sets of six measurements. Repeatability assessed using the intraclass correlation coefficient was satisfactory [23]. For the group as a whole, the variability assessed with the CoV in 3 year olds was similar to that obtained in 5 year olds and adults [12, 16, 17, 19], and no more variable than for other commonly obtained physiological parameters in children [24]. There are several possible explanations for the poor variability observed in three of the 3 year olds in the present study. R_{int} was measured while the individual breathed through a transparent oronasal mask with the mouth slightly open; it was, however, difficult to determine whether the children were nose or mouth breathing and whether a consistent breathing pattern was maintained between each set of measurements. Spontaneous switching between oral and nasal routes is one possible reason for the variability. For clinical use, R_{int} methods have to rely upon the collection of $P_{mo(t)}$ curves during quiet breathing. Inevitably, effects due to respiratory muscle activity [25, 26] and to upper airway compliance [27] can distort the pressure signal. Uncontrollable movement of the tongue or variations in the size of the glottic aperture could all have had a substantial influence on the upper airway geometry and, hence, led to measurement variability. Most of the children could be persuaded to accept a mouthpiece, but many experienced difficulty in maintaining an adequate seal. The design of an appropriate mouthpiece with a flanged edge to prevent leaks and incorporating a noseclip, may reduce the variation of the measurement of R_{int} in 3 year olds.

A source of nonbiological variability may have been introduced from the design of the interrupter device itself. This incorporates a single transducer which is used to measure airflow as a function of recorded pressure prior to interruption and mouth pressure immediately after interruption. Consequently, the device is preprogrammed to activate valve closure using a particular flow (in this case 0.2 L·s^{-1}) and, therefore, the exact flow which coincides with valve closure is unknown. This could potentially cause measurement error.

Currently, there is no fully validated method of assessing the response to bronchial challenge in this age-group. The P_{tc,O_2} method had been shown to be a robust method and more reliable and sensitive than the advocated FOT in the presence of moderate bronchoconstriction in young asthmatic children [9]. The P_{tc,O_2} was, therefore, considered to be the most suitable choice for assessing the response to bronchial challenge in this study. In comparison to R_{int}, which is a measurement of airways resistance, the fall in P_{tc,O_2} after administration of bronchoconstrictor is thought to reflect ventilation/perfusion ratio (V'/Q') inequality [6]. Although it is known that the primary cause of V'/Q' mismatch after challenge stems from airway narrowing, it is not clear whether it is the peripheral or central airways which are responsible. Nevertheless, falls in P_{tc,O_2} and increases in total lung resistance measured using the FOT generally correlate after bronchoconstriction [1, 9], and therefore P_{tc,O_2} can be used to indirectly assess reductions in airways calibre.

The concentration-response curves obtained for P_{tc,O_2} were more consistent than those obtained using R_{int}; all subjects achieved a significant change in P_{tc,O_2} from baseline at a concentration prior to the maximum concentration of methacholine administered, as previously demonstrated in 5 year olds after methacholine challenge [12]. It had been expected that R_{int} would be equally as sensitive in 3 year old as in 5 year old children, but the SI values for the 3 yr old group were lower than in the 5 year olds (3 yrs geometric mean (range) 3.0 (1.0–6.6); 5 yrs 4.2 (1.4–11.4)) [12]. Following a ≥15% fall in P_{tc,O_2} in 3 year olds, R_{int} had changed by a threshold of >2 SI in 10 of the 12 subjects. The remaining two subjects obtained a SI index of 1.4 and 1.0. In contrast, the response to bronchoconstrictor measured using P_{tc,O_2} changed by more than 7 SI in all subjects.

There are several factors which may contribute to the lack of sensitivity of R_{int} in the 3 year olds. Since the interrupter technique relies upon the measurement of mouth pressure to represent alveolar pressure (P_{alv}), the presence of airway obstruction may retard equilibration and lead to underestimation of the latter [28–30]. Bates *et al.* [14] and Ludwig *et al.* [31] reported that in normal, tracheotomized, paralysed anaesthetized, open-chested dogs, the pressure recorded at the trachea is virtually identical to that of P_{alv} after airflow interruption. This implies that R_{int} is effectively a measurement of airway resistance in the open-chest model. After the animals were treated with histamine aerosols, significant regional differences in P_{alv} were noted [31]; however, it was concluded that under these conditions R_{int} continued to be a useful reflection of the flow resistance of the overall airway tree. This has recently been confirmed by Smith *et al.* [32] after methacholine challenge in rabbits.

Based on model studies, Bates *et al.* [27] estimated that an increase of up to 10 times in airway resistance would still be correctly measured by the interrupter technique if compliance of the upper airways is not excessively high. We have previously shown [16] that in spontaneously breathing adults the prediction of Bates *et al.* [27] is essentially true, and is in agreement with data reported by others [33] and in other situations in adults [34]. Also, under controlled conditions in the laboratory, R_{int} was capable of detecting a significant (>2 SI) change in 9 out of 10 asthmatic children aged 5 yrs at a level to change P_{tc,O_2} by >15%. The prediction of Bates *et al.* [27], however, cannot be extrapolated to 3 year old children as the approximate initial pressure appears to underestimate the pressure change required to calculate resistance after moderately induced bronchoconstriction. Although we have shown that R_{int} is capable of detecting the bronchial response to methacholine at the maximal concentration administered, responses obtained at submaximal concentrations were unreliable in many of the 3 year old children. This interrupter device cannot, therefore, be advocated for measuring gradual responses to bronchoprovocation in this age-group under these conditions.

The compliant extrathoracic airway which includes the cheeks and floor of the mouth, reduces the change in P_{mo} due to dissipation of pressure after interruption [27, 28]. Both effects will result in underestimation of true R_{int}. In the present study, support of the most distensible part of the upper airways, the cheeks, was provided by the inflated cuff of the oronasal mask, which projected beyond the centre of the cheeks. The mask itself increased the dead space volume of the interrupter valve by 20–25 mL, introducing another small potential source of error in the measurement [20].

The method of R_{int} calculation involved a linear back-extrapolation of two discrete portions of the $P_{mo(t)}$ curve located in the second half of the trace. This form of analysis is probably most sensitive to traces which have a relatively horizontal or linear second portion. Any concavity with respect to the x axis will tend to cause an underestimation of R_{int}. In contrast to adults, preschool children have "knee-shaped" curves even under baseline conditions, which become progressively more exaggerated after induced obstruction [12], indicating poor equilibration between P_{mo} and P_{alv}. The analysis of the slow second pressure change by Bates *et al.* [27] indicates that in tracheostomized animals with normal lungs the main contribution to this pressure change is stress relaxation of the lung tissues and chest wall [35]. However, in the presence of airway narrowing, a further component of the second pressure change results from gas redistribution between parallel pathways (pendelluft) [31]. Additionally, there may also he continuing respiratory muscle activity (increasing P_{alv}). Therefore, this form of R_{int} analysis of the $P_{mo(t)}$ curve may not be optimal for this age-group. Values of P_{mo} taken from a later part of the curve may provide better sensitivity but are of unknown physiological significance [17].

The reversal of airflow obstruction after administration of a bronchodilator was clearly detected using R_{int}. In every subject, the value of R_{int} after salbutamol was significantly lower than the baseline value (mean (SD) baseline 0.91 (0.20) $kPa \cdot L^{-1} \cdot s$; after salbutamol 0.78 (0.19) $kPa.L^{-1} \cdot s$; $p<0.05$). These results are in agreement with those reported in adults with reversible airways disease [19], in which R_{int} was shown to be as sensitive as body plethysmography in detecting changes in airway resistance following administration of a bronchodilator.

Few other lung function techniques have been applied in 3 year olds. Forced expiratory manoeuvres are effort-dependent and restricted to only the most co-operative young child. The determination of R_{int} calculated from a linear back-extrapolation technique appears promising at least for detecting an improvement in airway calibre; and, hence, may find use in bronchodilator trials in preschool children where few other direct techniques exist. Measurements with a specially designed mouthpiece to reduce baseline variability coupled with maximal upper airways support may improve the sensitivity of R_{int} for challenge testing. Refinements in the $P_{mo(t)}$ analysis may also be beneficial. The measurement of a fall in P_{tc,O_2}, as shown previously, provides a reliable indicator of induced bronchoconstriction.

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