

PEDIATRICS

Opening interrupter technique in pre-school children with chronic respiratory diseases: a perspective case-control study in the diagnosis of airway hyperresponsiveness

Giovanna Vitaliti, MD, Salvatore Leonardi, MD, and Mario La Rosa, MD

*Operative Unit of Pediatric Pneumology, Allergology and Cystic Fibrosis, University of Catania, Catania, Italy***Abstract**

Background: Optimal treatment for pediatric respiratory diseases is strictly related to follow-up evaluations of lung function. The aim of our study was to show the efficacy of the Opening Interrupter Technique in diagnosing the presence of airway obstruction in pre-school children. **Materials and methods:** Our study was a prospective case-control study, evaluating 82 patients affected by asthma and/or cystic fibrosis (CF) and 50 healthy pre-school children, as control group. All patients were 3- to 5-years old and they were followed by our Pediatric Department, University of Catania, Italy, from February 2011 to June 2012. Measurements of respiratory resistance (o-Rint) by the opening interrupter technique were made with the MasterScreen PFT device, Jaeger GmbH, Würzburg, Germany, during quiet breathing. The presence of airway obstruction was detected as a value of o-Rint higher than two standard deviations (SD) compared with the theoretical data. **Results:** We found higher values of o-Rint in asthmatic patients than in the control group, with a high statistical difference ($p < 0.0001$). The same results were found when we compared patients with CF and the control group ($p < 0.0001$). Nevertheless, we did not find any significant statistical difference between respiratory resistances measured in asthmatic and patients with CF ($p > 0.05$). There was a significant inverse correlation between o-Rint and height only in asthmatic and patients with CF, but not in healthy controls ($p < 0.05$). **Conclusions:** In our study, the opening interrupter technique was efficient in detecting the presence of obstruction in chronic patients affected by asthma and CF.

Keywords

Airway resistances, opening interrupter technique, preschool children

History

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Introduction

Clinical follow-up, including lung function evaluations, is necessary for an optimal treatment of respiratory diseases above all in children affected by chronic diseases. Giving this evaluation is usually difficult in early infancy, in 3- to 5-year-old children, when their cooperation in respiratory tests, such as spirometry, is unsatisfactory. For this reason, in recent years, the interrupter technique has been considered a valid test to measure respiratory resistances, as little cooperation from children is required [1]. In asthmatic patients, the presence of obstruction is evident as FEV1 decreases when a spirometry is performed. The same result can also be evident in cystic fibrosis (CF) patients. These data cannot be recorded in pre-school children, as they usually can not perform an adequate spirometry. Nevertheless, the presence of bronchial obstruction can be recorded in this age group as an increase of “Respiratory resistance” defined as a difference between

mean alveolar pressure and airway opening pressure divided by flow measured at mouth [2,3].

The interrupter technique assumes that immediately after airflow interruption, mouth pressure equilibrates with alveolar pressure [2,3]. When this equilibrium is achieved, the mouth pressure equals the alveolar pressure. The interrupter resistance (Rint) can be calculated from various estimates of alveolar pressure based on the mouth pressure during occlusion [4–8]. The most frequently used estimates are represented by a linear back-extrapolation of 2 points, at 30 and 70 ms post occlusion to the point at 15 ms post occlusion [5,6] and the measure of the end-interruption pressure. For this analysis, flow could be measured both before and after the valve closure [7] (*opening interrupter technique*), in order to avoid too long intervals between the measurements of pressure and airflow [8]. In our study, the *opening interrupter technique* was used to measure airway respiratory resistances in pre-school children. Pressure was measured at the end of the interruption time, while flow was recorded after the opening of the occluding valve, which was aimed to increase the time necessary to equilibrate alveolar and mouth pressures, especially in children affected by chronic respiratory diseases.

Correspondence: Giovanna Vitaliti, University of Catania, AOU Policlinico-Vittorio Emanuele, via Santa Sofia n. 78, 95100 Catania, Italy. Tel: 0039 3404710614. E-mail: giovitaliti@yahoo.it

The aim of our study was to evaluate the efficacy of the Opening Interrupter Technique in diagnosing the presence of the obstruction in pre-school children affected by chronic respiratory diseases (asthma and CF).

Materials and methods

Our study was a prospective case–control study, evaluating 82 patients affected by asthma and CF and a control group composed of 50 healthy pre-school children. All patients were 3- to 5-years old and they were admitted to our Pediatric Pneumology, Allergology and CF Department, University of Catania, Italy, from February 2011 to June 2012. The Review Board of the University of Catania, Italy, gave the consent to all authors to access patients' data.

In the present study, all patients affected by intermittent or persistent wheezing and/or asthma, in the absence of corticosteroid, beta2-agonist and leukotriene antagonist therapy, for almost 2 months, were included. These patients had interrupted the above-mentioned therapies 2 months before the test was performed. Moreover, we included all pre-school children affected by CF in a good health period in absence of exacerbations and who had interrupted the antibiotic therapy 2 months before the test performance, followed by our referral centre since birth, in absence of the above mentioned therapy.

Parents of asthmatic children were asked to fill the ISAAC II questionnaire (Study of Asthma and Allergy in Childhood) [9], in order to state the eventual presence of familiar atopy, smokers among family members, to describe the respiratory symptoms of their child and to list eventually assumed therapies.

The diagnosis of CF was based on the positive result of the neonatal screening performed on the 3rd and the 15th day after the birth and on the positive result of the sweat chloride test, considered positive for chloride levels higher than 60 mEq/L.

In the control group, all pre-school children (aged 3–5 years) admitted to our Operative Unit with symptoms and signs not involving the respiratory system (urticaria, diarrheal, abdominal pain, conjunctivitis, atopic dermatitis, growth retardation) were included.

In the present study, children under 3 years of age and over 6 years of age, under corticosteroid, beta2-agonist and leukotriene antagonist therapy and patients affected by neurologic and chronic cardio-pulmonary diseases were excluded.

Measurements of respiratory resistances (o-Rints) by the *opening interrupter technique*, flow-volume curves and pressure-time curves were made with the same device (MasterScreen PFT, Jaeger GmbH, Würzburg, Germany). O-Rint level was measured during quiet breathing, according to the International Guidelines [10]. These measurements were performed by an expert technician and were then evaluated by a pediatric pneumologist physician. Technically satisfactory results were selected by eyeballing [11], and as the pressure-time and flow-time curves could be visualized, measurements showing aberrant pressure relative to flow were not retained. In general, the technique was well tolerated by children and five occlusions gave sufficient results in most cases. Before performing the test, an informed consensus was obtained by children's parents.

The presence of airway obstruction was detected when the value of o-Rint was higher than 2 SD compared with the theoretical data. The predictive values were automatically calculated by the o-Rint device, extrapolating them according to the weight and height of every single patient. Rint was calculated as the ratio of the mouth pressure transient assessed at the end of a 100-ms occlusion (DPm) to the flow recorded 70 ms after the opening of the occluding valve (V'): $Rint = DPm/V'$. The ratio under the value of one was considered by the device as a normal predictive values that varied from a range of 0.30 to 0.90 according to the height and weight of every patient.

In case of a child refusal to perform the technique or a failure in correct measurement after more than 10 attempts, the result of the test was considered as “absence of compliance”. Data were collected prospectively. All measurements were performed in the presence of one or both parents, who gave their informed consent.

Data analysis and statistics

o-Rint was expressed as absolute value (media and standard deviation (SD)). Comparisons between groups were made using Student's *t*-test for paired samples, as values were normally distributed. Correlations between two parameters were assessed by linear regression analysis. Significance was set at the 5% level. A *p* value <0.05 was considered as statistical significant. Analysis of SD for o-Rint was calculated using the Z-score.

Results

The demographic data of the patients included in our study are described in Table 1. The case group consisted of 72 asthmatic patients and 10 children with CF, while the control group consisted of 50 healthy patients.

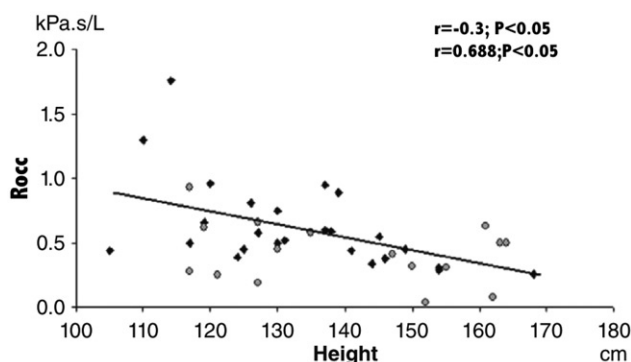
The analysis of the results was based on the best acceptable measurements of o-Rint calculated as the mean of five technically satisfactory sequential measurements. The test was repeated twice with a 10 min distance between the first and the second performance, in order to ensure its correctness above all in younger children (3 years of age) and to allow these children to feel confident with the device. We found higher values of o-Rint in asthmatic patients than in the control group, with a high statistical difference (first measure: 1.62 ± 0.38 versus 0.87 ± 0.18 kPa*s/L; second measure: 1.61 ± 0.43 versus 0.88 ± 0.21 kPa*s/L, respectively; $p < 0.0001$) (Table 2). The same results were obtained when the patients with CF and the control group were compared (first measure: 1.68 ± 0.48 versus

Table 1. Demographic features of patients included in our study.

	Healthy patients (n = 50)	Asthmatic patients (n = 72)	Cystic fibrosis patients (n = 10)
Gender (male = M and female = F)	M = 33, F = 17	M = 38, F = 34	M = 6, F = 4
Age (years)	4.66 ± 1.30	4.19 ± 0.96	4.3 ± 0.67
Weight (kg)	20.31 ± 4.54	18.87 ± 4.70	17.85 ± 3.42
Height (cm)	112.47 ± 9.81	106.87 ± 14.84	99.05 ± 34.10
O-rint (kPa*s/L)	0.87 ± 0.18	1.62 ± 0.38	1.68 ± 0.48

Table 2. Comparison between the airway resistances (Rocc) measured in our asthmatic and patients with CF and in healthy controls.

	First measure, kPa*s/L	Second measure, kPa*s/L	<i>p</i> Value ^a
Healthy control versus asthmatic children	0.87 ± 0.18 versus 1.62 ± 0.38	0.88 ± 0.21 versus 1.61 ± 0.43	<i>p</i> < 0.0001
Healthy control versus children with CF	0.87 ± 0.18 versus 1.68 ± 0.48	0.88 ± 0.21 versus 1.90 ± 0.71	<i>p</i> < 0.0001
Asthmatic versus children with CF	1.62 ± 0.38 versus 1.68 ± 0.48	1.61 ± 0.43 versus 1.90 ± 0.71	ns ^b

^aStudent *t*-test.^bns, not statistically significant difference.Figure 1. Correlation between the difference Rocc (respiratory resistance measured by the opening interrupter technique) and height, in the asthmatic and children with cystic fibrosis. (●) Asthmatic ($r = -0.3$; $p < 0.05$); (◆) cystic fibrosis ($r = -0.688$; $p < 0.05$).

0.87 ± 0.18 kPa*s/L; second measure: 1.90 ± 0.71 versus 0.88 ± 0.21 kPa*s/L, respectively; $p < 0.0001$) (Table 2). Nevertheless, we did not find any significant statistical difference between the asthmatic and the patients with CF (first measure: 1.62 ± 0.38 versus 1.68 ± 0.48 kPa*s/L, respectively; second measure: 1.61 ± 0.43 versus 1.90 ± 0.71 kPa*s/L, respectively; $p > 0.05$).

There was a significant inverse correlation between o-Rint and height only in asthmatic and patients with CF, but not in healthy controls ($r: -0.300$, $p < 0.05$ in asthmatic patients; $r: -0.688$; $p < 0.05$ in patients with CF); that is, the younger the child was, the greater o-Rint resulted, but only in case of a presence of clinical and instrumental of obstruction (Figure 1). The same inverse correlation was not found between o-Rint and weight in the three groups.

In our study, we found that the Opening Interrupter Technique had been performed easily, with a rate of execution of 62% in 3-year-old children and 100% in 4- and 5-year-old children. The number of interruptions was calculated as a mean number of interruptions: 9.2 interruptions (ints) in 3-year-old children and 9.6 (ints) in 4- and 5-year-old children. The percentage rate of successful performances was 79%.

Discussion

The results of our study show that the Opening Interrupter Technique is efficient in diagnosing the presence of airway

obstruction in patients affected by chronic respiratory diseases, such as asthma and CF. As a matter of fact, in our study we found higher values of o-Rint in asthmatic and children with CF than in the control group. The difference was statistical significant ($p < 0.0001$).

To our knowledge, in the literature there is only one study by Oswald-Mammosser et al. in 2010 [1], describing the technique (Opening Interrupter Technique) and comparing it with traditional Rint and body Plethysmography. The authors studied 32 asthmatic patients and 11 children with CF, aged 5–18 divided into 2 groups: Obstructed (Obs) and Non-obstructive patients (NObs). Airway resistances were measured in all patients by all the above-mentioned techniques (Opening Interrupter Technique, RINT and Plethysmography). In their study, the authors found that respiratory resistances were higher in the obstructed group than in non-obstructed children when measured by Plethysmography, but not by Rint and Opening Interrupter Technique. Therefore, they did not find any statistical difference of respiratory resistances in Obs and NObs children when measured by Rint and Opening Interrupter Technique. In addition, they found that both Opening Interrupter Technique-Plethysmography and Rint-Plethysmography resistances were inversely correlated with the severity of obstruction. Finally, they also found a significant bronchodilator response only for respiratory resistances measured by the Opening Interrupter Technique. The authors explained that Rint baseline values were not different between the Obs and NObs groups and they partly attributed it to the fact that NObs children were younger and had higher Rint values, when compared with the older children, with higher Rint levels merely linked to the disease itself.

Thus, the authors concluded that Rint (either Opening Interrupter Technique and traditional RINT) may be less sensitive than Plethysmography for detecting obstruction at baseline. Nevertheless, when bronchodilator tests were performed, a response was detected with the Opening Interrupter Technique in some children in whom Plethysmography also decreased significantly, confirming that the Opening Interrupter Technique was more sensitive in detecting the obstruction after a bronchodilator test. The same results were previously found by Davies et al. [12], who demonstrated that airway resistances measured by Rint and spirometer FEV1 reflect different aspects of the lung function.

Our study shows some differences if compared to the Oswald-Mammosser's paper. First of all, the range of the examined sample is more restricted. In fact, we had included only pre-school children, aged between 3 and 5 years old, considering that the anatomical lung development during childhood and adolescence is different and it could represent a confounding parameter for the final results. In our study, we found a high significant difference of o-Rint levels between obstructive (asthmatic and patients with CF) and non-obstructive children (healthy controls) ($p < 0.0001$). This result underlines the importance of Opening Interrupter Technique in efficient detecting of obstruction when the examined group is equally distributed. Our patients, in fact, were all 3-to-5-year-old children and auxologic parameters (weight and height) of all included children were equally distributed. This result may show that the Opening Interrupter

Technique is more sensitive to an equal distribution of auxologic parameters when compared with other techniques. On this regard, we found that there was an inverse correlation between respiratory resistances and height in asthmatic and children with CF ($r: -0.300, p < 0.05$ in asthmatic patients; $r: -0.688; p < 0.05$ in patients with CF), but this inverse correlation was not found in healthy controls. The same results were described by Oswald-Mammosser in her study and are in line with literature data. These data may be related to the elastance of the pulmonary tissues. Lanteri and Sly [13] observed the same results relating them to the initial rapid increase in pressure after occlusion that decreased with height to the power function of -1.29 , whereas total respiratory resistance, measured after a 2.5-s airway occlusion, decreased by the power function of -1.71 . The authors explained their findings as a dysynaptic growth in younger children, with compliance increasing more rapidly than the decrease in respiratory resistance [13]. A lung increased elastance may lead to higher o-Rint values in young children, and it may explain the higher o-Rint values in younger children.

Finally, we made a comparison between children affected by chronic respiratory diseases and healthy controls. In fact, in the study of Oswald-Mammosser Obstructive children were considered asthmatic and patients with CF in a good health phase, when they were free of symptoms and chronic therapy. Nevertheless, the airway epithelium remodelling is always present in children affected by chronic respiratory diseases, independently from the phase of their disease. Therefore, even if the asthmatic or CF child does not show any symptoms of his/her chronic disease, the airway and lung remodelling is still present. In addition, it has been demonstrated in the literature that airway anatomic modifications are different in children affected by Asthma or CF than in healthy patients, and this remodelling starts 4 years before the onset of symptoms, during a sub-clinical phase of the respiratory disease [14–16]. This hypothesis could explain the significant difference between the airway obstruction (o-Rint) measured in asthmatic and children with CF and in healthy controls.

Nevertheless, in our study we did not find any difference in o-Rint levels between Asthmatic patients and CF ones. A limit to our study was a small number of patients with CF; however, we could only include this number of children considering a relatively moderate incidence of this disease. In our referring centre, the majority of children were older or younger than the range we considered (3-to-5-years old). Anyway, even if we considered this group as a separate one, we also found increased o-Rint values in patients with CF with respect to the healthy controls, confirming their peculiar lung function disease even in younger children.

Conclusions

In conclusion, we can affirm that considering that the bronchial and the lung remodelling develops 4 years before the onset of symptoms in patients affected by chronic respiratory diseases [14–16], the measure of respiratory resistances is important for an early diagnosis and follow-up of chronic respiratory diseases, above all in early childhood. The Opening Interrupter Technique, allowing a longer time for equilibration of the mouth and alveolar pressures, especially in obstructed children, in our study was efficient

in detecting the presence of obstruction in chronic patients. It is also to be considered that in literature there are only few studies on this innovative technique and further studies should clarify its relevance in diagnosing airway obstruction, with data on its sensitivity and specificity under different condition (i.e. with bronchodilator and methacoline tests).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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