

Functional assessment of allergic asthmatic children while asymptomatic

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ABSTRACT

The aim of this study was to detect the best test lung function to identify abnormalities in asthmatic children while asymptomatic. We studied 200 asthmatic children. Patients were evaluated by questionnaire to evaluate the presence of symptoms and drug consumption in the previous 3 months. Allergological evaluation by skin-prick tests and seric-specific IgE determination for relevant local inhalant allergens was made. Lung function was studied evaluating expiratory flows and measuring lung volumes by nitrogen washout technique. One hundred twenty-seven of 200 (63%) children showed functional abnormalities: 21 (10.5%) children had flow reductions, 56 (28%) children had volume modifications, and 50 (25%) children had either flow and lung volume alterations, respectively. We observed increased total lung capacity (TLC), residual volume (RV), and ratio RV/TLC values more often in patients with mild and moderate persistent asthma than in patients with intermittent asthma. No significant difference was detected considering expiratory flows. Measurements of lung volumes are an important tool to evaluate "air trapping" in asthmatic patients and this could be related to disease severity. According to the literature, our data suggest that an increase of RV, functional residual capacity RV/TLC could be the only functional airway dysfunction present in asthmatic children during asymptomatic period.

(Allergy Asthma Proc 27:359–364, 2006; doi: 10.2500/aap.2006.27.2922)

Respiratory function tests are an important tool in the diagnosis and management of asthmatic children.¹ In adolescent asthmatic patients² and even in young children^{3,4} spirometry results are usually a primary outcome measurement. The forced expiratory volume in 1 second (FEV₁) is linearly related to the severity of airway obstruction, and a positive acute FEV₁ response to bronchodilator of >12% helps to confirm the diagnosis of asthma.⁵ In asthmatic patients without evident clinical signs, forced expiratory flows at small lung volumes (forced expiratory flow at 25–75% [FEF_{25–75}]) may provide evidence of persisting obstruction^{6,7} and bronchial hyperresponsiveness.⁸ However, parameters such as mid-expiratory flow at 25 at 50% of vital capacity (MEF₂₅ and MEF₅₀) show a great variability between measurements.⁹ Furthermore, the effort's independence of these parameters has been questioned.¹⁰ Measurement of lung volumes is important to detect dysventilatory syndromes and

may provide confirmatory data as well as additional data to spirometry.^{5,11–13}

The aim of this study was to evaluate lung function performances such as static lung volumes: residual volume (RV) functional residual capacity (FRC), and total lung capacity (TLC) or forced expiratory flows (FEV₁, MEF₅₀, MEF₂₅, and MEF_{25–75}) in asymptomatic asthmatic children.

PATIENTS AND METHODS

Two hundred asthmatic children, as defined by the American Thoracic Society (ATS),¹⁴ (140 boys and 60 girls) aged (mean $\pm$ SD) 9.3 ± 3.5 years, were recruited for the study. All children were regularly followed at the outpatient Pneumology Clinic of the Department of Pediatrics of the University of Chieti. They were recruited according to their characteristics corresponding to the inclusion criteria. Only children in good clinical control (no clinical evidence of exacerbation of asthma symptoms) as suggested by clinical history in the 3 months preceding the study were admitted. All children were investigated by International Study of Asthma and Allergies in Children questionnaire¹⁵ with additional questions concerning nocturnal symptoms, exercise-induced asthma, and pharmacologic treatments in last 3 months.

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Clinical and Pharmacologic Assessment

The clinical assessment was done according to Global Initiative on Asthma (GINA) guidelines: intermittent episodic asthma (asthma level 1 [AL1]), mild persistent asthma (AL2), moderate persistent asthma (AL3), and severe persistent asthma (AL4).¹⁶ Pharmacologic therapy performed 3 months before the study was scored according to the class of therapy (from 0 to 9) in the following way: antihistamines or cromones = 1; long-acting β 2-agonists or montelukast = 2, inhaled corticosteroids = 3.

Functional Evaluation

Respiratory function was studied by expiratory flow measurement (FEV_1 , MEF_{25-75} , MEF_{25} , and MEF_{50}), using FEV_1 /volume curves, and by static lung volume measurement (RV, FRC, and TLC) using the nitrogen washout method.¹⁷ For the study, a pneumotachograph with an open circuit N₂ washout method (VMAX22L SensorMedics, Viasys Healthcare, Yorba Linda, CA) was used. Expiratory flow values were calculated as a percentage of the theoretic values for height.¹⁸

FEV_1 and peak expiratory flow (PEF) <85% of predicted, MEF_{25-75} , MEF_{25} , and MEF_{50} <70% of predicted were considered as pathological. Lung volume values were calculated as a percentage of the predicted values for height, according to Zapletal.¹⁹ TLC, FRC, and RV were considered pathological if <80% and >120%, and ratio RV/TLC was considered abnormal if >30%.

Tidal volume and inspiratory capacity (IC) had been measured during a normal respiratory cycle. Forced vital capacity (FVC) was calculated by a forced expiratory capacity maneuvers, and expiratory reserve volume (ERV) was calculated as difference between FVC and IC ($ERV = FVC - IC$). FRC has been measured with open circuit N₂ washout technique, with the patient breathing at tidal volume in 100% O₂ air, at FRC level, as described by Morris.²⁰ The RV was calculated as $FRC - ERV$, and TLC was calculated as $VC + RV$. The reliability of the tests was assessed according to recommendations of ATS and European Respiratory Society Statement.²¹

Statistical Analysis

Data were expressed as means $\pm$ SD, and a value of $p < 0.05$ was considered as significant. The percentage of patients with alterations of expiratory flows and lung volumes was calculated. Student's *t*-test was used to compare the means of the functional variables measured, between the group of patients with intermittent episodic asthma and groups with persistent asthma (mild, moderate, or severe).

Ethical Approval

The study was approved by the local Hospital Ethical Committee and written informed consents were

obtained by children's parents or guardians. The study did not receive any funding by Companies. The study was performed with internal University funding.

RESULTS

The mean duration of asthma was 4.4 ± 3.4 years. The mean asymptomatic period was 9.6 ± 1.3 months. All the patients showed one or more positive responses to local relevant allergens with a good concordance between skin-prick test and radioallergosorbent test results. Eighty-one children were monosensitized (46 children were monosensitized to mites and 35 children were monosensitized to pollens), 119 children were polysensitized for two or more respiratory allergens tested (grass, parietaria, ragweed, mites, dog and cat danders, and molds). Among our asthmatic children, 160 patients were found to have intermittent asthma (AL1), 34 patients had mild persistent asthma (AL2), and 6 patients had moderate persistent asthma (AL3). No child with severe persistent asthma (AL4) was found. The mean asthma level score was 1.2 ± 0.4 . All patients were treated with pharmacologic therapy according to GINA guidelines. The mean pharmacologic score was 2.1 ± 1.8 .

As a whole population, our asthmatic children had mean normal values of expiratory flows: $FEV_1 = 100 \pm 14\%$, $PEF = 93 \pm 24\%$, and $MEF_{25-75} = 90 \pm 24\%$; and lung volumes: $TLC = 100 \pm 18\%$, $FRC = 108 \pm 35\%$, $RV = 116 \pm 63\%$, and $RV/TLC = 25 \pm 9$. However, in the evaluation of individual patients, normal flows and volumes were found in only 73 children (36.5%). On the contrary, different patterns of functional alterations were observed in the remaining 127 (63%) patients. In particular, different patterns were found: (i) obstructive disease (21 children, 10.5%) with flow reduction and normal volumes, (ii) hyperinflated pattern (42 children, 21%) with RV and FRC increased and normal flows, (iii) mixed obstructive and hyperinflated disease (32 children, 16%) with flow reductions and RV and FRC increased, (iv) restrictive pattern (14 children, 7%) with volume reductions with normal flows, and, finally, (v) a mixed obstructive/restrictive pattern (18 children, 9%) with flow and volume reductions. Twenty-one patients presented significantly increased alterations of TLC, RV, and ratio RV/TLC in the mild and moderate patient groups. In comparison to results of patients in the intermittent group, this just failed to be significant for TLC ($p = 0.05$), but significant for RV ($p = 0.02$) and for ratio RV/TLC ($p = 0.04$). However, no significant difference was detected for expiratory flows between the three groups (Table 1). No significant difference was observed with regard to comparison with the AL3 group, probably because of the paucity of the subject number present in the group.

The sensitivity of spirometric tests (number of subjects with pathological test) in detecting functional

Table 1 Respiratory function tests divided according to GINA classification of asthma in 200 asthmatic children

Asthma Level	AL1	AL2	AL3	p Value (AL1 vs AL2)
No. of subjects	160	34	6	
FEV ₁	100.4 ± 14.6%	102.8 ± 15.7%	88.4 ± 14.3%	NS
PEF	95.4 ± 25.6%	88.5 ± 19.3%	78.6 ± 17.4%	NS
MEF ₂₅₋₇₅	91 ± 23.6%	93.8 ± 27.6%	68.2 ± 28.6%	NS
TLC	99.2 ± 16.4%	105.7 ± 23%	107.6 ± 19.4%	0.05
FRC	105.6 ± 32%	116.4 ± 42.6%	101.4 ± 13.46%	NS
RV	110 ± 54.2%	136 ± 88.7%	140.2 ± 75.6%	0.02
RV/TLC (%)	24.1 ± 9.2	27.8 ± 10.4	29.2 ± 2.19	0.04

Values are expressed as mean ± SD (percentage of predicted value).
AL1 = intermittent asthma; AL2 = mild asthma; AL3 = moderate asthma.

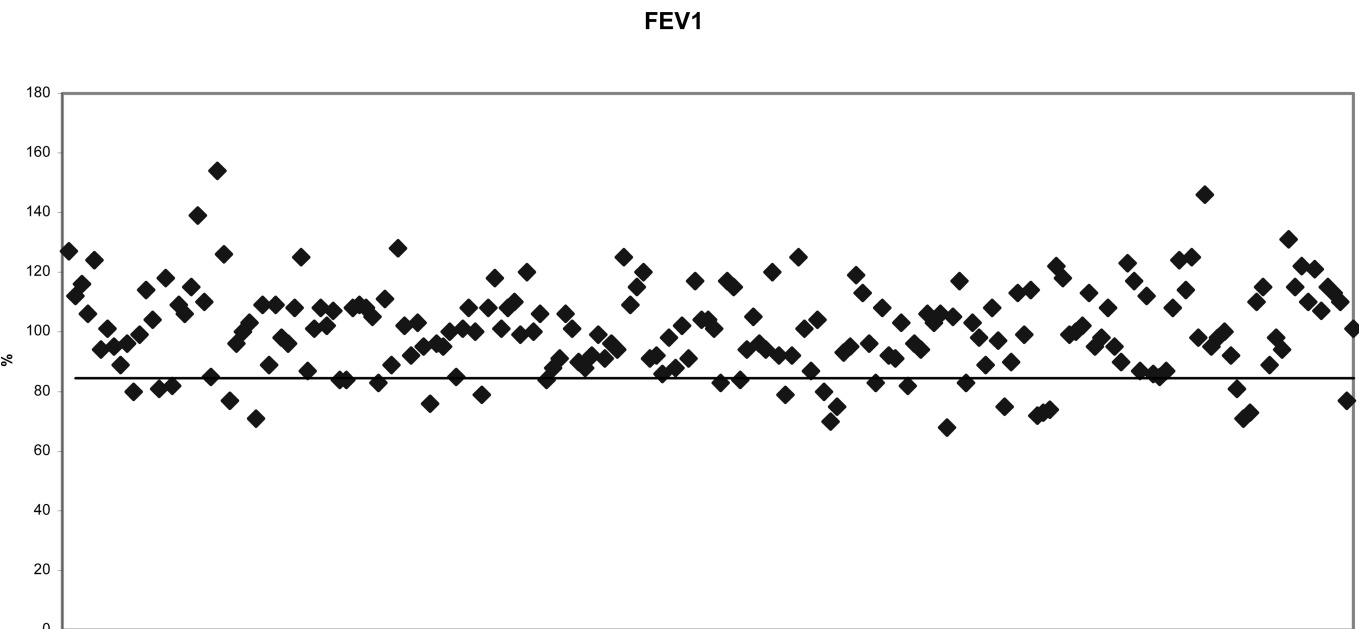


Figure 1. FEV₁ values expressed as percentage of predicted in 200 asthmatic children (38 patients below 85%).

abnormalities in our population of asymptomatic asthmatic patients showed the following results for expiratory flows: FEV₁, 19% (pathological values in 38/200; Fig. 1); MEF₂₅, 26% (pathological values in 53/200); MEF₂₅₋₇₅, 20% (pathological values in 40/200; Fig. 2).

The analysis of lung volume abnormalities showed TLC alterations in 68 patients (34%; decrease in 33 and increase in 35) and FRC modifications in 87 patients (43%; (decrease in 33 and increase in 54; Fig. 3). The Motley index (ratio, RV/TLC), hyperinflation sign, was pathological in 83 cases (41%).

DISCUSSION

In asthmatic children, significant abnormality in lung function may be present without any clinical symp-

toms of the disease and this has been suggested to be followed by lung hyperinflation.¹ Spirometry with determination of expiratory flows is the most used technique to assess respiratory function in children.^{1-4,22} FEV₁ is linearly related to the severity of airways obstruction,⁵ and it is less susceptible to errors and variability than MEF₅₀ and MEF₂₅.⁹ Measurement of absolute lung volumes is one of the pulmonary function tests that may provide confirmatory data to forced expiratory spirometry.⁵ It has been reported that RV is the most sensitive parameter to depict persistent airflow obstruction in asymptomatic children and the relation of RV to TLC often is increased in asthmatic patients in remission.^{23,24} Our data are in agreement with these studies, concerning the utility of lung volume assessment, especially RV and Motley index (RV/

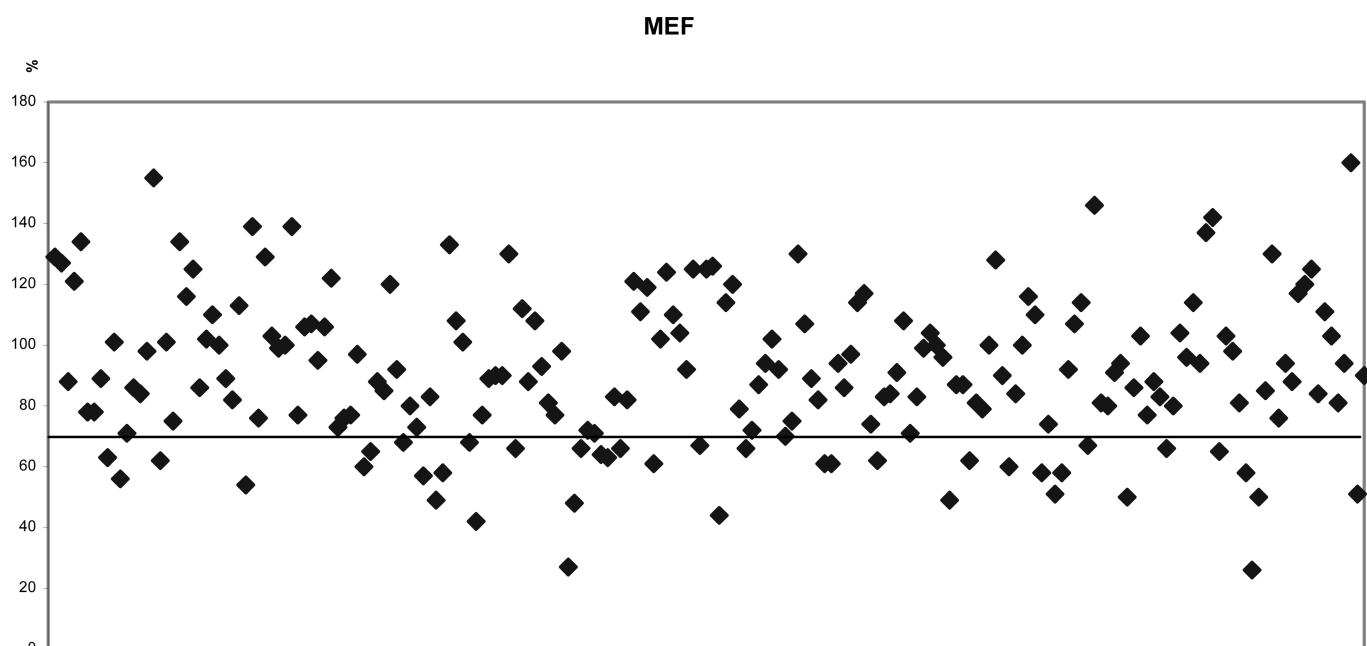


Figure 2. MEF Values expressed as percentage of predicted in 200 asthmatic children (40 patients below 70%).

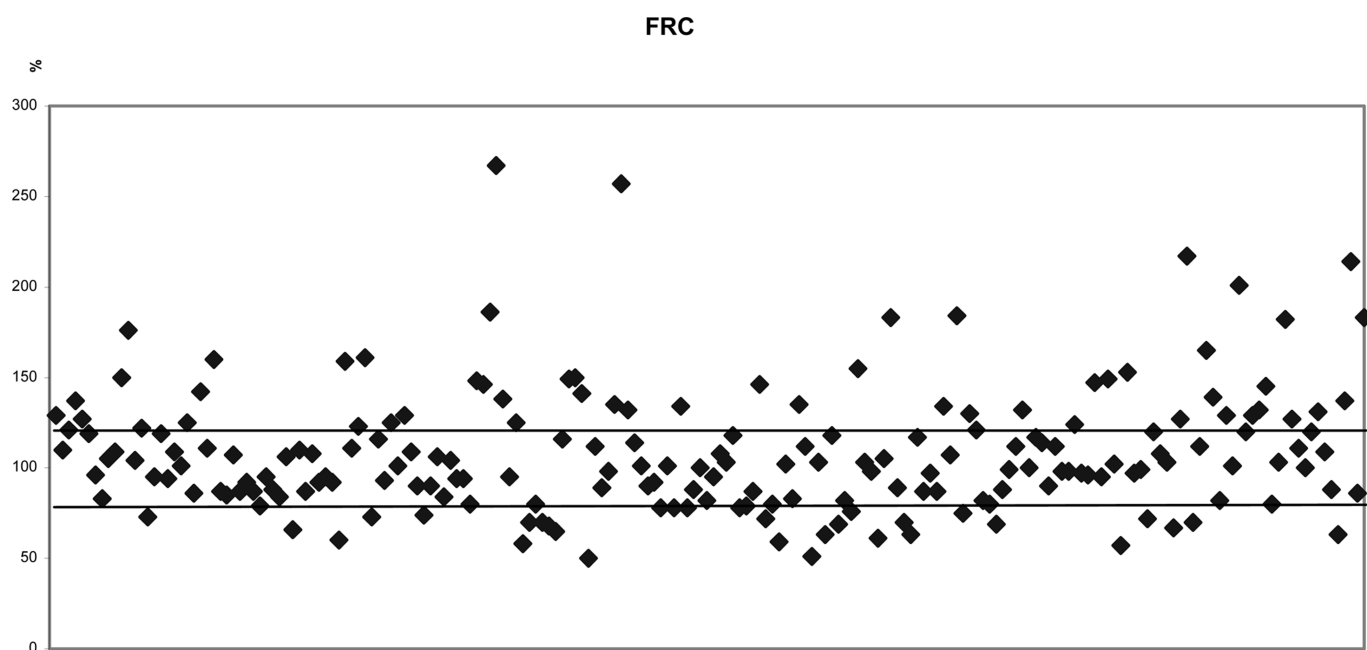


Figure 3. FRC values expressed as percentage of predicted in 200 asthmatic children (54 patients over 120% and 33 patients below 80%).

TLC), to detect "air-trapping" in asthma.^{19–21,25} Additional studies would be of interest to evaluate in the follow-up the significance of the RV abnormalities in term of relapse or loss of lung function.

In our study, flow reductions have been detected in 71 (35.5%) patients, and increased lung volumes have been observed in 74 (37%) children, in 42 of whom hyperventilation was the unique lung function abnormally. This finding confirms and further expands the concept that lung volume measurement is more sensitive than expiratory flow evaluation in asymptomatic

asthmatic patients. Particularly, increased RV and RV/TLC ratio allow the identification of a latent bronchial obstruction, even in the presence of normal spirometry values.²⁴ These modifications are a sensitive index of "air trapping," consequent to lung inflammation^{26,27} and effectively are predictive for a positive response to methacholine in asthmatic patients with normal spirometry results.²⁸ Furthermore, in children with stable asthma, an increase in RV was found to be significantly correlated with urinary leukotriene E4 levels²⁹ and with presence of atopy.³⁰ On the contrary, the decrease

of RV was found to be associated with allergen avoidance and with reduction in sputum eosinophil levels.^{26,27}

Major increases in RV and FRC generally are found in children with severe asthma.³¹ In agreement with this, we also found greater values of TLC, RV, and RV/TLC in patients with moderate than in patients with mild and intermittent asthma. The obstruction of small airways and the loss of elastic recoil, resulting in premature closure of the airway, may be the main causes of increases in FRC and RV¹¹ and these phenomena obviously are related to increasing asthma severity and distal lung dysfunction.³² The distal airway involvement in asthma also may explain the observation that an RV decrease, after bronchodilation test, has higher positive predictive value than an FEV₁ increase, for an early diagnosis of asthma^{33,34} and very likely also for its persistence.³⁵ In our study population there also is a little number of children with pure restrictive (7%) or mixed obstructive-restrictive (9%) functional patterns. This may be the result of an anatomic or constitutional lung conformation,³⁶ which may be concomitantly present with asthma or a reduction in the lung development consequent to a chronic hypoventilation. Thus, lung volume evaluation may be useful to detect true restrictive lung disorders because a "restrictive impairment" can be diagnosed with spirometry in asthmatic patients as a consequence of a reduced forced ERV, *i.e.*, the ERV measured from the FVC maneuvers and preceding tidal breath.³⁷

In conclusion, our data confirm and further extend the concept that an increase in RV and RV/TLC ratio can be the only functional alteration during the interval phase of the disease and may be an index of incomplete control. Hyperinflation seems to cause minimal overt clinical symptoms³³ but may be responsible for loss of elastic recoil. If this results in greater risk of asthma relapse after remission needs to be evaluated in long-term longitudinal studies.

REFERENCES

- Bye MR, Kerstein D, and Barsh E. The importance of spirometry in the assessment of childhood asthma. *Am J Dis Child* 146:977-978, 1992.
- Enright PL, Linn WS, Avol EL, et al. Quality of spirometry test performance in children and adolescents. Experience in a large field study. *Chest* 118:665-671, 2000.
- Eigen H, Bieler H, Gant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med* 163:619-623, 2001.
- Crenesse D, Berlioz M, Bourrier T, and Albertini M. Spirometric in children aged 3 to 5 years: Reliability of forced expiratory maneuvers. *Pediatr Pulmonol* 32:56-61, 2001.
- Enright PL, Lebowitz MD, and Cockcroft DW. Physiologic measures: Pulmonary function tests. Asthma outcome. *Am J Respir Crit Care Med* 149:S9-S18, 1994.
- Coates JE. Lung function in disease. In *Lung Function. Assessment and Application in Medicine*, 4th ed. Oxford: Blackwell Scientific Publications, 388-456, 1979.
- Lebecque P, Kiakulanda P, and Coates AL. Spirometry in the asthmatic child: Is FEF₂₅₋₇₅ a more sensitive test than FEV₁/FVC? *Pediatr Pulmonol* 16:19-22, 1993.
- Currie GP, Jackson CM, Lee DK, and Lipworth BJ. Determinants of airway hyperresponsiveness in mild asthma. *Ann Allergy Asthma Immunol* 90:560-563, 2003.
- Coates AL, Desmond KJ, Demizio D, et al. Sources of error in flow-volume curves. Effect of expired volume measured at the mouth vs that measured in a body plethysmograph. *Chest* 94:976-982, 1988.
- Krowka MJ, Enright PL, Rodarte JR, and Hyatt RE. Effect of effort on measurement of forced expiratory volume in one second. *Am Rev Respir Dis* 136:829-833, 1987.
- Stanescu D. Small airways obstruction syndrome. *Chest* 116:231-233, 1999.
- Irvin CG. Lung volume: A principle determinant of airway smooth muscle function. *Eur Respir J* 22: 3-5, 2003.
- Irvin CG, Pak J, and Martin RJ. Airway-parenchyma uncoupling in nocturnal asthma. *Am J Respir Crit Care Med* 161:50-56, 2000.
- ATS Board of Directors. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. November 1986.
- Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): Rationale and methods. *Eur Respir J* 8:483-491, 1995.
- Liard R, Leynaert B, Zureik M, et al. Using global initiative for asthma guidelines to assess asthma severity in population. *Eur Respir J* 16:615-620, 2000.
- Tepper RS, Merth IT, Newth CJL, and Gerhardt T. Measurement of functional residual capacity in infants by helium dilution and nitrogen wash-out techniques. In *Infant Respiratory Function Testing*. Stocks J (Ed)., London, U.K. 1996.
- Manzke H, Stadlober E, and Schellauf HP. Combined body plethysmographic, spirometric and flow volume reference values for male and female children aged 6 to 16 years obtained from "hospital normals." *Eur J Pediatr* 60:300-306, 2001 (Abs).
- Zapletal A. Lung Function in Children and Adolescents. Karger (Ed). 4-12, 1987.
- Morris MG. The open circuit nitrogen washout technique for measuring the lung volume in infants: Methodological aspects. *Thorax* 54:790-795, 1999.
- Quanjer PhH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. *Eur Respir J* 16(suppl):5-40, 1993.
- Brown LK. Pulmonary function testing in bronchial asthma: Standard and emerging techniques. *Mt Sinai J Med* 58:507-520, 1991.
- Pool JB, Greenough A, Gleeson JGA, and Price JF. Persistent lung hyperinflation in apparently asymptomatic asthmatic children. *Respir Med* 83:433-436, 1989.
- Cooper DM, Cutz E, and Levison H. Occult pulmonary abnormalities in asymptomatic asthmatic children. *Chest* 71:361-365, 1977.
- Stocks J, and PH Quanjer. Reference values for residual volume, functional residual capacity, and total lung capacity. *Eur Respir J* 8:492-506, 1995.
- Peroni DG, Piacentini GL, Vicentini L, et al. Effective allergen avoidance reduces residual volume and sputum eosinophils in children with asthma. *J Allergy Clin Immunol* 108:308, 2001.
- Peroni DG, Piacentini GL, Costella S, et al. Mite avoidance can reduce air trapping and airway inflammation in allergic asthmatic children. *Clin Exp Allergy* 32:850-855, 2002.
- Stanbrook MB, Chapman KR, and Kesten S. Gas trapping as a

- predictor of positive methacholine challenge in patients with normal spirometry results. *Chest* 107:992–995, 1995.
29. Severien C, Artlich A, Jonas S, and Becher G. Urinary excretion of leukotriene E4 and eosinophil protein X in children with atopic asthma. *Eur Respir J* 16:588–592, 2000.
 30. Gruber W, Eber E, Steinbrugger B, et al. Atopy, lung function, and bronchial responsiveness in symptom-free paediatric asthma patients. *Eur Respir J* 10:1041–1045, 1997.
 31. Bevegard S, Eriksson BO, Graff-Lonnevig V, et al. Respiratory function, cardiovascular dimension, and work capacity in boys with bronchial asthma. *Acta Paediatr Scand* 65:289–296, 1976.
 32. Kraft M, Pak J, Martin RJ, et al. Distal lung function at night in nocturnal asthma. *Am J Respir Crit Care Med* 163:1551–1556, 2001.
 33. Kraemer R, Meister B, Schaad UB, and Rossi E. Reversibility of lung function abnormalities in children with perennial asthma. *J Pediatr* 102:347–350, 1983.
 34. Walamies MA. Diagnostic role of residual volume in paediatric patients with chronic symptoms of the lower airways. *Clin Physiol* 18:49–54, 1998.
 35. van den Toorn LM, Overbeek SE, Prins JB, et al. Asthma remission: Does it exist? *Curr Opin Pulm Med* 9:15–20, 2003.
 36. Kennedy JD, Robertson CF, Olinsky A, et al. Pulmonary restrictive effect of bracing in mild idiopathic scoliosis. *Thorax* 42:959–961, 1987.
 37. Miller A. A simple spirometric clue to asthma: Airways obstruction suggested by negative or reduced forced expiratory reserve volume despite normal FEV₁-FVC ratio. *Mt Sinai J Med* 57:85–92, 1990. □

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