Significant bronchodilator response in FEF25-75 for the diagnosis of asthma in children

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Abstract

Introduction: A spirometry with a significant bronchodilator response (SBDR) in FEV1, a methacholine concentration that produces a 20% drop in FEV1(PC20) [?] 2 mg/ml and a positive exercise test (ET), have high specificity for the diagnosis of asthma in children. The value of FEF25-75 in spirometry has been questioned. The objective of this study was to relate SBDR in FEF25-75 of spirometry with normal FEV1 and FEV1/FVC, with bronchial hyperresponsiveness (BHR) to methacholine or exercise in children aged 5 to 15 years with clinical suspicion of asthma. Material and method: Cross-sectional study of spirometries performed between January 2017 and December 2019 in children aged 5-15 years with suspected asthma, who had a methacholine and/or exercise test within a period not exceeding 60 days. It was analyzed using STATA 14-0 and Microsoft Excel 2016 applying Chi-square tests. Results: The average age was 9.04 years (range: 5 – 14 years), 56.17% male. Of 324 spirometries with normal FEV1 and FEV1/FVC, 66 (20.4%) presented SBDR at FEF25-75. 47% and 33.3% of the children with and without RSB in FEF25-75, respectively, had PC20 [?] 2 mg/ml and/or positive TE (p = 0.0396). Conclusions: children with suspected asthma and normal spirometry, with SBR in FEF25-75, had greater BHR than those without SBDR in FEF25-75. The SBDR in FEF25-75 was not always accompanied by an BHR that can confirm the diagnosis of asthma with high probability.

INTRODUCTION

Confirming the diagnosis of asthma in children by demonstrating variable expiratory flow limitation, expressed by a significant bronchodilator response (SBDR) or the presence of bronchial hyperresponsiveness (BHR) to methacholine or exercise, avoids over and underdiagnosis[(1–4)]. The finding of an SBDR in spirometry, defined as a bronchodilator change [?] 12% in FEV_1, confirms the diagnosis of asthma in a child with clinical suspicion, without the need for other studies [(4)].

The methacholine test (MT) measures BHR directly and has high sensitivity and low specificity for the diagnosis of asthma, which increases with lower PC20 (methacholine concentration that produces a 20% drop in FEV_1) [(2)]. A PC20 between 4 and 8 mg/dl is considered borderline, and below 4 mg/dl, the lower the PC20, the greater the possibility of diagnosing asthma in patients with clinical suspicion of this disease [(5,6)].

The exercise test (ET) is an indirect bronchial provocation test, which has low sensitivity and high specificity for the diagnosis of asthma. A positive ET is considered to be a drop in FEV_1 [?] 10% post-exercise [(7)].

Although SBDR in spirometry, a PC20 [?] 2 mg/dl and a positive ET measure different pathophysiological aspects, all three indicate with high probability the presence of asthma [1,2,7].

In recent years, the value of FEF_{25-75} and forced expiratory flows have been questioned in the interpretation of spirometry, because flow values depend on the volume at which they are measured and have high variability [8].

Spirometry has low sensitivity for the diagnosis of asthma[9]. Frequently, spirometry in children with suspected asthma is often normal, without SBDR in FEV_1, but with SBDR in FEF_{25-75} (>30%), without a >5% change in FVC (which indicates that the curves pre and post bronchodilator were measured at similar volumes). This result, in a child with clinical suspicion of asthma, raises doubts in its interpretation, due to the publications that suggest that the FEF_{25-75} does not contribute to clinical decisions[8,10]. Despite this, this parameter is still frequently used [11].

We postulate that if the only SBDR in FEF_{25-75} in the spirometry, of children with suspected asthma, indicates a reversible obstruction of the airway that allows to certify the diagnosis, it will be more frequently associated with a BHR in the MT and/or ET than , in children with normal spirometry, without SBDR in FEF_{25-75}.

Due to the fact that the evidence is not conclusive regarding the role of FEF_{25-75} for the evaluation of spirometry, this study aims to relate SBDR to FEF_{25-75}, when FEV_1 and FEV_1/FVC are normal, with MT and/ET, in children aged 5 to 15 years with clinical suspicion of asthma.

MATERIAL AND METHOD

A cross-sectional study with an analytical component was carried out, without direct intervention on the study subjects.

The study population was children aged 5 to 15 years with clinical suspicion of asthma, who underwent spirometry and MT or ET within a period of 60 days, in the pulmonary function laboratory of Clínica INDISA, from January 2017 to December 2019.

Spirometry was performed according to national and international standards, with an MGC Diagnostics ® equipment, and only those that met the acceptability and reproducibility criteria were included[12,13]. Multiethnic reference values were used for their interpretation [14]. The MT was carried out with the technique of increasing concentrations of Cockcroft and the PC20[5,15] was determined. The ET was performed on a treadmill at submaximal heart rate, with humidity and environmental temperature control, with subsequent measurement of the percentages of fall in FEV_1 with respect to baseline at 3, 5, 10, and 15 minutes post-exercise [16].

We worked on an anonymized database, which identified each child with a number (ID), age (in years, months) and if he was using inhaled corticosteroids at the time of the exam, height, weight, clinical diagnosis, and date performance of spirometry, MT and TE. The lower limit (LI) and Zscore of FEV_1, FEV_1/FVC, FVC, FEF_{25-75}, % change with the bronchodilator in FEV_1, FEF_{25-75} and FVC were recorded from the spirometries. The PC20 and the percentage of maximum drop in FEV_1 in the ET were verified.

All these data from the reports of these tests appear in the manual and computerized records of the Clínica INDISA lung function laboratory.

Children who obtained a bronchodilator response (BDR) [?] 30% in FEF_{25-75} (SBDR) were compared versus those who obtained a BDR < 30% with normal FEV_1, FEV_1/FVC, in relation to the MT and ET in each patient.

The STATA 14.0 statistical package and Microsoft Excel 2016 software were used for data analysis. A descriptive analysis of the variables of interest was made and Chi-square tests were used to analyze the groups in relation to their results in the MT and ET. A p value less than 0.05 was considered statistically significant.

To carry out this project, authorization was obtained from the Medical Directory of the Clinica INDISA and the approval of the Bioethics Committee of the Andres Bello University.

RESULTS

Between January 2017 and December 2019, spirometries were performed on 470 children under 15 years of age with clinical suspicion of asthma at the INDISA Clinic. Of these, 416 children had spirometry plus MT and/or ET performed in an interval of less than 2 months. Among the reports of this group studied, there were 6 spirometries with obstructive report without SRBD in FEV_1, 17 obstructive reports with SBDR in FEV_1, 38 normal with SRBD in FEV_1 and the vast majority, 355, with normal spirometry without SBDR in FEV_1. In this last group, 324 spirometries showed a variation in FVC between the pre- and post-bronchodilator value of less than 5%. Figure 1 details the flowchart of pulmonary function tests.

The mean age of the children was 9.04 years (SD: 2.67 years; Range: 5 – 15 years), and 56.17% were boys. In 37.04% the use of corticosteroids was reported, 33.02% were not using it and in 29.94% it was not possible to obtain that information. The detail of the socio-demographic and clinical information of the patients is shown in Table 1.

194 children underwent MT, 224 ET, and 94 had records of both tests.

The MT was positive (PC20 $<$ 8 mg/dl) in 135 children (69.6%), of which 103 (53.1%) had a PC20 [?] 2 mg/dl. The ET had a positivity of 11.6% (26 of 224 children).

Of the 42 children with SBDR in FEF_{25-75} and TM performed, 28 had a PC20 [?] 2 mg/dl; in 7 a PC20 between 2 and 8 mg/dl; and in another 7, a PC20 $>$ 8 mg/dl.

Similarly, of the 152 children without SBDR in $FEF_{25-75}$and MT performed, 75 had a PC20 [?] 2mg/dl; in 25 between 2 and 8 mg/dl; and in 52 $>$ 8 mg/dl.

On the other hand, among the children who presented negative MT (91), 14 (15.4%) showed an SBDR in FEF_{25-75} in the spirometry previously performed.

Figure 2 shows the positivity to MT and/or ET, between the comparison groups according to the presence or absence of SBDR in the FEF_{25-75}. When applying the chi-square test, it was found that this difference was statistically significant between both comparison groups (p value = 0.0396).

DISCUSSION

We found that children with suspected asthma and normal spirometry, with SBDR in FEF_{25-75}, have greater bronchial hyperreactivity demonstrated in MT and/or ET than those who, having normal spirometry, do not have SBDR in FEF_{25-75}. Despite this difference, we observed that the SBDR alone in FEF_{25-75} is not always accompanied by a HRB that can confirm the diagnosis of asthma with other exams, such as a PC20 [?] 2 mg/dl in the MT and/or a positive ET. It was even possible to rule out the diagnosis of asthma in 14 children with SBDR in FEF_{25-75}, due to a PC20 greater than 8mg/dl in the MT, which has a high negative predictive value for this pathology [(4)]. This finding suggests that the SBDR alone in FEF_{25-75} would not be sufficient in all cases to establish the diagnosis of asthma, unlike what happens with the finding of SBDR in FEV_1, which always confirms the diagnosis [(4,17)]. We cannot rule out that these 14 results are false negative MT, which can occur when the patient is in an asymptomatic period or is on inhaled corticosteroids, which may have influenced the results of some children, although both conditions did not change between spirometry and the MT.

One of the reasons that may explain the lack of correlation between HBR and SBDR in FEF^{25-75} in some children studied, is that the spirometric curves before and after bronchodilator are not performed at iso-volume, and that the SBDR in FEF^{25-75} responds to this change in volume and not to a real response, since the measurement of the flows are dependent on the lung volume at which they are measured[(8)]. Serial measurements of FEF_{25-75} in the same individual can change due to the progression or improvement of lung disease due to changes in lung volume[(8)]. Although only spirometries with a change of less than 5% between

pre- and post-bronchodilator FVC values were included in the study to avoid this effect, it is not enough to demonstrate that the measurements were made at isovolume, since FVC is not only determined by the expired volume, but also the effect of gas compression during the forced expiration maneuver, which is more important in patients with airway obstruction [18].

Another factor that can determine a false SBDR in only FEF_{25-75} is the poor quality of the spirometric curves, especially when the child is not capable of performing a maximum effort, which would be more frequent at a younger age [8].

The diagnostic value of SBDR in FEF_{25-75}, when the rest of the parameters are normal and there is no SBDR in FEV_1, has not been described in the literature, although it has been suggested that a response of at least 30% in FEF_{25-75} is more sensitive for identifying asthmatics than a 12% response in FEV_1 [9,19].

For a long time, FEF_{25-75} was considered a parameter with greater sensitivity than FEV_1 to assess early small airway obstruction (SAO) in children [20]. In recent years it has been shown that expiratory flows, including FEF_{25-75}, are not very useful in clinical practice, both in adults and children [8,10]. They are also not more sensitive in detecting SAO in children diagnosed with asthma and cystic fibrosis as previously described [10].

As reported in the literature, we found a very low sensitivity of FEV_1 to determine variable airway obstruction in asthmatic children [9].

The MT presented a sensitivity of almost 70% to detect BHR. Although it is not a very specific test for diagnosing asthma, half of the children in the study with positive TM showed PC20 [?] 2 mg/dl, which highly likely supports this diagnosis [2,5].

ET showed a lower sensitivity than that reported in the literature, which can be explained by the use of inhaled corticosteroids and the conditions of humidity (average 34.8%) and temperature (20.5 degC) in which it was performed [7,16]. This is a finding to take into account for our pulmonary function laboratory, since it is performed very frequently and, in our study, it proves to have very little utility, since a negative exercise test does not rule out the diagnosis of asthma [7].

One of the limitations of this study is given by the lack of a subsequent analysis of the evolution of the patients to confirm or rule out the diagnosis of asthma and thus be able to relate it to the results of the studies carried out. Another limitation is that it is a retrospective study, in which the indication to request the MT and ET was not controlled and varied with the criteria of each pediatric bronchopulmonary who requested the studies in each patient.

We conclude that children with suspected asthma and normal spirometry, with SBDR in FEF_{25-75} studied here, have greater bronchial hyperreactivity than those who, having normal spirometry, do not have SBDR in FEF_{25-75}. The SBDR in FEF_{25-75} is not always accompanied by an HRB that can confirm the diagnosis of asthma.

The sensitivity of the SBDR of the spirometry and exercise test for the diagnosis of asthma were very low, being higher for the MT. We believe that in our laboratory it would be more efficient to perform a MT than a TE to assess HRB in children with suspected asthma.

REFERENCES

1. 2020 GINA Main Report - Global Initiative for Asthma - GINA [Internet]. [cited 2021 Feb 6]. Available in: *https://ginasthma.org/gina-reports/*
2. Coates AL, Wanger J, Cockcroft DW, Culver BH. Bronchoprovocation Testing Task Force: Kai-Hakon Carlsen the BTT, Diamant Z, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017;49(5):1601526.
3. Looijmans-Van Den Akker I, Van Luijn KRS, Verheij TJM. Overdiagnosis of asthma in children in primary care: A retrospective analysis. BR J Gen Pract. 2016;66(644):e152–7.

4. Gaillard EA, Kuehni CE, Turner S, Goutaki M, Holden KA, de Jong CCM, Lex C, H Lo D, Lucas J, Midulla F. European Respiratory Society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years. Eur Respir J 2021;2004173.
5. Cockcroft DW. Direct Challenge Tests. Chest 2010;138(2):18S-24S.
6. Selvanathan J, Aaron SD, Sykes JR, Vandemheen KL, FitzGerald JM, Ainslie M, Lamier C, Filed S, MCIvor A, Hernandez P, et al. Performance Characteristics of Spirometry With Negative Bronchodilator Response and Methacholine Challenge Testing and Implications for Asthma Diagnosis. Chest 2020;158(2):479–90.
7. Hallstrand TS, Leuppi JD, Joos G, Hall GL, Carlsen K-H, Kaminsky DA, Coates AL, Cockcroft DW, Culver BH, Diamant Z, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J 2018;52(5):1801033.
8. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25-75% and FEF75% does not contribute to clinical decision making. Eur Respir J 2014;43(4):1051–8.
9. Mallol J, Riquelme C, Aguirre V, Martinez M, Gallardo A, Sanchez C, Cordova P. Value of bronchial reversibility to salbutamol, exhaled nitric oxide and responsiveness to methacholine to corroborate the diagnosis of asthma in children. Allergol Immunopathol (Madr). 1 de mayo de 2020;48(3):214–22.
10. Lukic KZ, Coates AL. Does the FEF $_{25-75}$ or the FEF $_{75}$ have any value in assessing lung disease in children with cystic fibrosis or asthma? Pediatr Pulmonol 2015;50(9):863–8.
11. Cottini M, Lombardi C, Berti A CP. Small-airway dysfunction in paediatric asthma. Curr Opin Allergy Clin Immunol 2021 Apr 1;21(2)128-134.
12. Caussade S, Saavedra M, Barrientos H, Linares M, Aguirre V, Puppo H, Lewinson D, Ubilla C, Meyer M, Moscoso G, et al. Comision Funcion Pulmonar Sociedad Chilena de Neumologia Pediatrica. Neumol Pediatr 2019 14(1): 41-51.
13. Graham BL, Steenbruggen I, Barjaktarevic IZ, Cooper BG, Hall GL, Hallstrand TS, Kaminsky D, MCCarthy A, MCCormakc M, Oropez C, et al. Standardization of spirometry 2019 update an official American Thoracic Society and European Respiratory Society technical statement. Am J Respir Crit Care Med 2019 ;200(8):e70-e88.
14. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, Enright P, Hankinson J, Ip M, Zheng J, Stocks J. ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J 2012 ;40(6):1324-43
15. Davis BE, Cockcroft DW. Past, present and future uses of methacholine testing. Expert Rev Respir Med 2012;6(3):321–9.
16. Anderson SD. 'Indirect' challenges from science to clinical practice. Eur Clin Respir J 2016;3(1):31096.
17. Danvers L, Lo DKH, Gaillard EA. The role of objective tests to support a diagnosis of asthma in children. Paediatr Respir Rev 2020;33:52-57
18. Pellegrino R, Antonelli A, Crimi E, Gulotta C, Torchio R, Dutto L, Pedersen O, Bursaco V. Dependence of bronchoconstrictor and bronchodilator responses on thoracic gas compression volume. Respirology. 2014;19(7):1040–5.
19. Ciprandi G, Gallo F, Cirillo I. FEF25-75 and Asthma in Clinical Practice. Iran J Allergy Asthma Immunol 2018;17(3):295–7.
20. Lebecque P, Kiakulanda P, Coates AL. Spirometry in the asthmatic child: is FEF25-75 a more sensitive test than FEV1/FVC? Pediatr Pulmonol 1993;16(1):19–22.

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