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Volumetric capnography to detect ventilation inhomogeneity in children and adolescents with controlled persistent asthma

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Abstract

Objectives: To study changes in the variables of volumetric capnography in children and adolescents with asthma compared with a control group and to investigate their changes with the use of bronchodilators and bronchial provocation test with methacholine.

Methods: One hundred and three patients with controlled persistent asthma and 40 healthy volunteers participated in the study. All of them underwent volumetric capnography and spirometry. All asthmatics repeated the tests after bronchodilator use. Among 103 asthma patients, 33 underwent methacholine challenge test, and measures were recorded on three occasions: before and after methacholine and after bronchodilator use.

Results: Compared with the control group, asthmatics had an increase in the slope of phase III normalized by tidal volume and decreases in tidal volume, forced expiratory volume in one second, forced vital capacity, rate of obstruction and forced expiratory flow between 25 to 75% of forced vital capacity. After bronchodilator use, there was an increase in spirometric variables, volume of anatomic dead space, and decrease in the slope of phase II normalized by tidal volume, but the slope of phase III normalized by tidal volume did not change. After methacholine, there was an increase in this variable, which decreased after bronchodilator use.

Conclusions: The increase in the slope of phase III normalized by tidal volume in asthma patients suggests that these patients have ventilation inhomogeneity in the distal air spaces, which may reflect chronic structural disorders or reversible acute changes seen on the bronchial provocation test.

J Pediatr (Rio J). 2011;87(2):163-168: Capnography, spirometry, pediatrics, asthma.

Introduction

The presence and severity of obstruction in asthma are conventionally assessed by forced expiratory volume in one second (FEV_1) measured by spirometry. However, the use of this test to evaluate small airways has been questioned. In addition, the individual being assessed must collaborate in order to perform the spirometry maneuvers, because they are highly dependent on effort and, therefore, difficult to be carried out by children[1,2].

Limitations of spirometry have motivated the search for markers capable of detecting early changes in the airways, as well as to detail dysfunctions of small airways. Studies assessing ventilation inhomogeneity using inert gases in

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the lungs show that they appear to be more sensitive than FEV_1 in the identification of changes in small airways in asthma both in adults and children.[1,3,4]

The pattern of elimination of carbon dioxide (CO_2) in expired tidal volume obtained by volumetric capnography (VC) makes it possible to calculate indices that can detect disturbances in the ventilation/perfusion ratio (V/Q). This method does not require forced maneuvering to be performed. VC has proved to be an alternative to evaluate pulmonary functional changes and its application in clinical research has become more accessible with the development of new technologies. In the pediatric population, measures of dead space using VC has been studied for two decades in patients intubated and ventilated.[5-10] In individuals breathing spontaneously, VC can be used to evaluate many diseases, especially when dealing with small airways.[11] Recent studies have shown a correlation between VC measurements and spirometry in adults with and without lung disease.[12-15] However, few studies have evaluated this tool in children,[16,17] especially in those with asthma.[18]

The objective of the present study was to evaluate VC measurements in asthmatic children and adolescents and to compare them with those of healthy individuals, as well as to investigate the changes in VC variables as a response to bronchodilator and bronchial provocation test (BPT) in asthmatics.

Methods

We conducted a prospective, observational and cross-sectional study from April 2007 to March 2010 in the Pulmonary Physiology Laboratory (LAFIP), Universidade Estadual de Campinas (UNICAMP), including 103 patients with persistent asthma followed-up at a hospital of the same institution, and a control group of 40 volunteers from 6 to 15 years of both sexes. Diagnosis and classification of mild, moderate or severe persistent asthma were established based on the Global Initiative for Asthma (GINA).[19] All patients showed positive immediate hypersensitivity skin test to at least one antigen tested and total serum immunoglobulin E above the 97.5 percentile for age in at least one blood sample. We excluded patients with asthma and concomitant chronic or acute cardiopulmonary disease, history of pulmonary lobectomy or segmentectomy, other chronic disease on systemic corticosteroids, congenital heart disease, or protein-calorie malnutrition.

All asthmatics were using corticosteroid dry powder inhaler (budesonide) at a dose of 400 to 800 mcg/day, and formoterol 12 mcg twice daily for a period of at least 30 days. Patients had neither a history of asthma attacks requiring hospitalization in intensive care unit during the previous year nor exacerbation or worsening of symptoms requiring increased use of inhaled bronchodilators or systemic corticosteroids 4 weeks before the tests. Asthmatics patients and the control group did not have symptoms or respiratory infections during the last 15 days before the date of the tests. First, all participants performed VC followed by spirometry, and the asthmatics repeated the two tests after using a bronchodilator (salbutamol, four jets of 100 mcg each). Of the 103 asthma patients, 33 underwent BPT with methacholine in a second visit.

Bronchial provocation test

BPT was performed according to the guidelines of the European Respiratory Society (ERS) and the American Thoracic Society (ATS).[20] We used acetyl-beta-methylcholine (Methacholine Chloride) code A2251 produced by Sigma Laboratory, diluted at concentrations of 0.125, 0.250, 0.5, 1, 2, 4, 8, 16 and 40 mg/mL. One minute after each concentration was inhaled, we measured FEV_1 , and the proof was discontinued when there was a decrease of 20% or more in FEV_1 compared to baseline. Spirometry and VC were analyzed before and after BPT and after reversion of the test using a bronchodilator. At these three times, we also measured oxygen saturation using pulse oximetry (SpO_2).

Volumetric capnography

We used the monitor of respiratory profile CO_2SMO-Plus® model DX-8100 (Novametrix, Wallingford, USA) and the software Analysis Plus!® for Windows 2000 to record the measurements and VC curves. Graphic tracings were obtained from the exhaled CO_2 compared to the expired volume and had three phases. Phase 1: removal of air from the mouth, trachea and bronchi, corresponding to the volume of anatomic dead space and, therefore, free of CO_2. Phase 2: rapid increase in the concentration of CO_2, it represents the transition between the gas exhaled between the airway and the alveolus. Phase 3: also called alveolar plateau phase, in which case the elimination of gas contained in the great mass of alveolus. Thus, it is possible to identify two different slopes in the tracing: the first phase, corresponding to phase II of the spirogram, is called slope of phase II; the second phase, corresponding to phase III of the spirogram, is called slope of phase III. Patients were instructed to remain seated with their back turned to the monitor, using a nose clip, and calmly breathing through a mouthpiece. After observing standards of respiratory pattern, we began the recording of capnographic variables for 5 minutes. After data collection, an off-line sequence of respiratory cycles of the patients was selected. Cycles in the first minute were excluded because this is considered a period of adaptation of the patient to the device. Next, the respiratory cycles with a VC curve showing an irregular shape, such as absence of the plateau for air leaks or depression of the plateau for cough, were excluded.[12] After that, we excluded the cycles whose coefficient of variation for expired tidal volume was higher or lower than 25% and for exhaled

CO_2 higher or lower than 5%.[14,18] The means of the variable in the remaining cycles were calculated and considered to be the final result. The variables were: respiratory rate (RR), expired tidal volume (VT) and alveolar tidal volume (VT_{alv}), anatomic dead space volume (VD_{anat}), VD_{anat}/VT, slope of phase II (slope2), and slope of phase III (slope3) of spirogram. Because expired volumes in children vary, standardizing slope2 and slope3 by tidal volume (slope2/VT and slope3/VT) is recommended to compensate for variations in the size of individuals.[18]

Spirometry

We used the spirometer CPFS/D model and the software BREEZE PF® Version 3.8 for Windows 95/98/NT (MedGraphics, Saint Paul, Minnesota, USA). The test was performed according to the guidelines of the ERS/ATS.[20] All asthmatics were instructed not to use bronchodilators for short or long duration 12 hours before the test. We selected the values of forced vital capacity (FVC), FEV_1, the index of obstruction (FEV_1/FVC) and forced expiratory flow between 25-75% of FVC (FEF_{25-75}).

Statistics

For analysis of the variables in the comparison between groups, we used the nonparametric Mann-Whitney test. For analysis of the comparison between the variables at two different times (before and after bronchodilator), we used the nonparametric Wilcoxon test. For analysis of the comparison at three different times (before and after methacholine and after bronchodilator), we used the analysis of variance (ANOVA) for repeated measures. For data processing, we used the software SPSS version 17.0. The level of significance was set at p values ≤ 0.05.

The study was conducted after approval by the Research Ethics Committee of the institution, no. 419-2005. All parents or guardians of children and adolescents participating in the study signed a consent form.

Results

Of the 103 asthmatics, 59 (57.3%) were males and 44 (42.7%) females. Sixteen (15.5%) were classified with mild asthma, 62 (60.2%) with moderate asthma, and 25 (24.3%) with severe asthma. In the control group, 17 (42.5%) were males and 23 (57.5%) females.

The anthropometric, spirometric and capnographic variables of the asthma group and control group are shown in Table 1. When compared with the control group, asthmatics had lower spirometric values of FEV_1, FEV_1/FVC and FEF_{25-75} ($p < 0.001$) and FVC ($p = 0.007$), and in relation to the VC, they showed higher slope3/VT ($p < 0.001$) and slope2/VT ($p = 0.044$) and lower VT ($p = 0.035$).

Table 1 - Distribution of median, minimum and maximum values, and comparison of anthropometric, capnographic and spirometric variables between asthmatics and healthy volunteers

Variables	Median (minimum-maximum)		p*
	Asthma group (n = 103)	Control group (n = 40)	
Age (years)	10.90 (6.21-15.56)	10.51 (6.52-15.01)	0.167
Weight (kg)	36.5 (15.8-65.5)	39.5 (18.6-89.3)	0.096
Height (cm)	143.5 (110.0-175.0)	147.0 (110.0-168.4)	0.613
RR (rpm)	18.9 (8.3-33.9)	20.2 (10-34.5)	0.388
VT (mL)	356.9 (195.7-1,359.1)	413.4 (244.1-1062.9)	0.011
VT_{alv} (mL)	274.5 (125.4-1,217.0)	291.2 (103.1-942.0)	0.092
VD_{anat} (mL)	77.3 (41.9-133.3)	84.5 (44.2-123.0)	0.071
VD_{anat}/VT	0.24 (0.10-0.36)	0.22 (0.12-0.31)	0.161
Slope2 (mmHg/L)	506.6 (267.0-1,051.1)	461.6 (255.7-857.3)	0.101
Slope3 (mmHg / L)	17.55 (5.6-51.9)	12.08 (4.5-27.7)	0.001
Slope2/VT	1.417 (0.199-4.833)	1.167 (0.347-2.888)	0.027
Slope3/VT	0.051 (0.004-0.264)	0.033 (0.004-0.111)	0.001
FEV_1†	84 (27-121)	102 (72-128)	0.001
FVC†	91 (53-145)	97 (77-120)	0.007
FEV_1/FVC%	79 (44-99)	91 (78-100)	0.001
FEF_{25-75}†	63 (9-171)	111 (56-159)	0.001

FEF_{25-75} = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RR = respiratory rate; slope2 = slope of phase II of the volumetric capnography curve; slope3 = slope of phase III of the volumetric capnography curve; VD_{anat} = anatomic dead space volume; VT = tidal volume, VT_{alv} = alveolar tidal volume.
* Mann-Whitney.
† Expected percentage.

The evaluation of 103 patients with asthma after bronchodilator use showed a significant increase in spirometric variables, VD_{anat} and VD_{anat}/VT and decrease in slope2 and slope2/VT ($p < 0.001$); however, there were no differences in slope3 and slope3/VT (Table 2).

BPT with methacholine was performed by 33 volunteers of the asthma group, 21 (63.6%) males and 12 (36.4%) females. After methacholine, we found a statistically significant decrease in FEV_1, FVC, FEV_1/FVC, FEF_{25-75} and SpO_2 ($p < 0.001$) and increased slope3/VT ($p = 0.003$). After reversion with a bronchodilator, there was increase in all spirometric variables and SpO_2 ($p < 0.001$) and decreased slope3/VT ($p < 0.001$) (Table 3). Figure 1 shows the changes in FEV_1 and slope3/VT at the three times of BPT.

Discussion

To our knowledge, this is the first study to evaluate the variables obtained by the volumetric capnography curve in children and adolescents with asthma compared with a control group, as well as the pharmacological effects of bronchodilators and bronchial provocation in the airways of these patients.

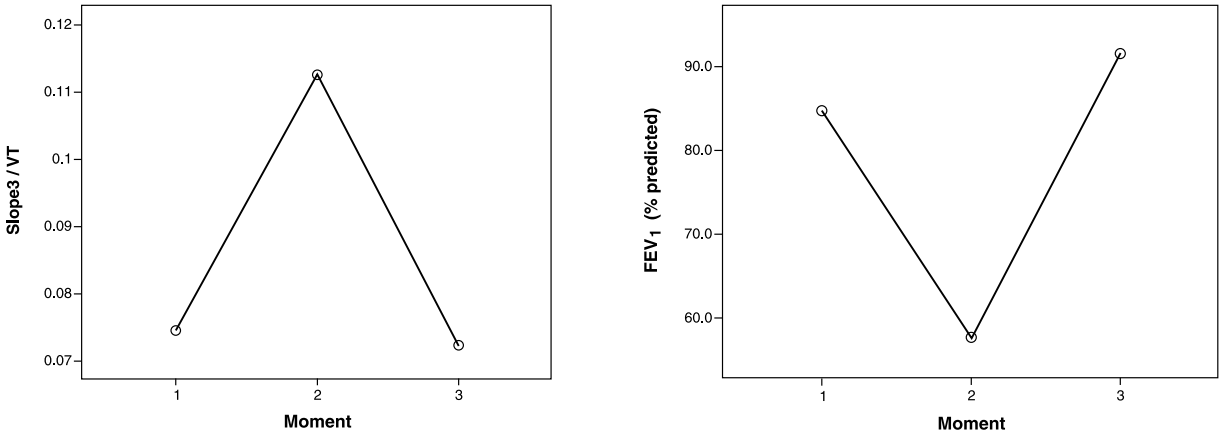

Figure 1 - Mean values of slope3/VT and FEV_1 at three times of the bronchial provocation test: moment 1, before methacholine; moment 2, after methacholine; and moment 3, after bronchodilator

Table 2 - Distribution of median, minimum and maximum values and comparison of variables of volumetric capnography and spirometry of the 103 asthmatics in two different times: before and after bronchodilator

Variables	Median (minimum-maximum)		p*
	Pre-bronchodilator	Post-bronchodilator	
RR (rpm)	18.9 (8.3-33.9)	18.7 (7.6-39.4)	0.545
VT (mL)	356.9 (195.7-1,359.1)	372.6 (194.5-1,436.0)	0.035
VT_{alv} (mL)	274.5 (125.4-1,217.0)	262.6 (37.4-1,196.7)	0.671
VD_{anat} (mL)	77.29 (41.9-133.3)	87.3 (51.6-156.1)	0.001
VD_{anat}/VT	0.24 (0.10-0.36)	0.26 (0.11-0.39)	0.001
Slope2 (mmHg/L)	506.6 (267.0-1,051.1)	464.5 (243.8-898.5)	0.001
Slope3 (mmHg/L)	17.6 (5.6-51.9)	18.6 (5.4-48.3)	0.261
Slope2/VT	1.417 (0.199-4.834)	1.308 (0.176-3.705)	0.001
Slope3/VT	0.051 (0.004-0.265)	0.056 (0.004-0.234)	0.111
FEV_1†	84 (27-121)	94 (32-142)	0.001
FVC†	91 (53-145)	95 (57-151)	0.048
$FEV_1/FVC\%$	79 (44-99)	85 (50-100)	0.001
FEF_{25-75}†	63 (9-171)	91 (15-180)	0.001

FEF_{25-75} = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RR = respiratory rate; slope2 = slope of phase II of volumetric capnography curve; slope3 = slope of phase III of the volumetric capnography curve; VD_{anat} = anatomic dead space volume; VT = tidal volume; VT_{alv} = alveolar tidal volume.
* Wilcoxon test.
† Expected percentage.

Table 3 - Distribution of mean and standard deviation values and comparison of the values of volumetric capnography and spirometry of 33 asthmatics at three moments of the bronchial provocation test with methacholine

Variables	Moment (mean + SD)			p*	
	1 (pre-BPT)	2 (post-BPT)	3 (post-Bd)	Time 1 to 2	Time 2 to 3
RR (rpm)	21.17±4.93	21.79±5.99	22.28±5.22	0.489	0.709
VT (mL)	354.2±124.4	356.4±142.5	386.4±163.1	0.905	0.069
VT_{alv} (mL)	282.7±127.3	288.6±146.3	289.9±144.0	0.770	0.914
VD_{anat} (mL)	69.5±14.2	66.46±15.5	77.0±16.0	0.103	0.001
VD_{anat}/VT	0.23±0.07	0.22±0.06	0.28±0.06	0.422	0.002
Slope2 (mmHg/L)	598.3±152.3	540.2±171.7	546.2±144.2	0.140	0.820
Slope3 (mmHg/L)	20.5±10.26	29.5±15.61	20.5±11.02	0.001	0.001
Slope2/VT	2.017±0.926	1.734±1.049	1.717±0.867	0.613	0.179
Slope3/VT	0.074±0.053	0.113±0.096	0.072±0.055	0.003	0.001
SpO_2 (%)	97.3±0.85	95.7±1.79	97.3±0.87	0.001	0.001
FEV_1†	84.76±15.42	57.55±14.08	91.52±14.58	0.001	0.001
FVC†	94.15±13.47	71.49±15.34	94.39±14.71	0.001	0.001
FEV_1/FVC%	80.15±8.92	71.88±12.46	86.36±7.79	0.001	0.001
FEF_{25-75}†	67.45±23.36	11.28±12.95	83.86±27.14	0.001	0.001

Bd = bronchodilator; BPT = bronchial provocation test; FEF_{25-75} = forced expiratory flow between 25 and 75% of FVC; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; RR = respiratory rate; SD = standard deviation; slope2 = slope of phase II of volumetric capnography curve; slope3 = slope of phase III of the volumetric capnography curve; SpO_2 = oxygen saturation by pulse oximeter; VD_{anat} = anatomic dead space volume; VT = tidal volume; VT_{alv} = alveolar tidal volume.
* Analysis of variance for repeated measures (ANOVA).
† Expected percentage.

In the present study, we found an increase in slope3/VT in asthmatic patients compared with the control group, suggesting ventilation inhomogeneity in the distal air spaces. Bourdin et al.[3] also found an increase in the slope of phase III of the nitrogen curve in asthmatic adults compared with the control group. Similarly to our study, they also found differences in FEV_1 between the groups. On the other hand Macleod et al.[2] found no changes in the indexes derived from the slope of phase III obtained with sulfur hexafluoride (SF_6) or in FEV_1, compared with children with controlled asthma and the control group.

After bronchodilator use, we found an increase in VD_{anat}, which confirms the findings of Steiss et al.,[17] who also observed an increase in the variable in children with moderate persistent asthma after bronchodilator use. The increase in the bronchial diameter might explain these findings.

Regarding slope2/VT, we found a greater value in asthmatics compared with controls, and a decrease in this variable after bronchodilator in asthmatics. Kars et al.[21] also found differences in rates obtained in phase II of the VC while comparing patients with emphysema and healthy adults. Unlike the slope3, slope2 is influenced by the anatomic dead space volume, because it represents the mixture of the air from the conduction airways and the air that participated in gas exchange.[11] Our results show a smaller slope2/VT when VT is increasing, as there is a slower rise in CO_2 in phase II because of increased volume of air that was eliminated in these patients, especially the volume of air that did not participate in gas exchange.

In the analysis of BPT, we found increased slope3/VT after inhalation of methacholine and decrease after bronchodilator. This finding may be caused by the asynchrony of emptying of alveolar units by the constrictor action of methacholine in peripheral airways. $FEF_{25-75,}$ which is the measurement of spirometry that better reflects the small airways, decreased after bronchial provocation, which reinforces this hypothesis. Verbanck et al.[22] previously found increase in the slope of phase III derived from the nitrogen curve in 20 healthy adults after BPT with methacholine. Olsson et al.[12] also found an increased slope of phase III in VC after bronchial provocation with methacholine in 19 healthy adults. These studies suggest that changes occur in the areas of gas exchange by the bronchoconstrictor effect. In the present study, there was a decrease in SpO_2 after methacholine. This variable showed an increase after reversion with bronchodilator, returning to baseline. These results reinforce the fact that bronchial provocation affects the V/Q ratio.

During the analysis of our results, we found changes in slope3/VT in asthmatics compared with healthy BPT, slope3/VT changed after methacholine, which were compatible with increased airway resistance and significant reversion after bronchodilator use. These results suggest that changes are fixed in asthmatic airways and are not reversible after bronchodilator use. However, there are reversible changes when bronchodilator use occurs after the acute episode of bronchoconstriction induced by methacholine.

Asthma in adults is characterized by structural and inflammatory changes[23,24] and by remodeling of both central and peripheral airways.[25] In lung biopsies, the presence of higher concentration of active eosinophils in small airways (bronchioles with diameters smaller than 2 mm) suggests that the periphery is the main site of obstruction in asthma.[26] Findings from high resolution computed tomography in adults with asthma also showed obstruction of large and small airways, in addition to subsegmental atelectasis, and air trapping, both related to the periphery of air spaces.[27] In children, other studies have found inflammatory changes in peripheral airway in autopsy tissue, particularly in severe asthma.[28] These data from the literature reinforce our hypothesis that asymptomatic children with controlled asthma show changes in the slope3, which may caused by structural changes and inflammatory airway disease.

Compared to spirometry, VC does not require maneuvers and can be easily performed by young children. It is also a small device that can be used in hospitalized patients, at outpatient clinics or at doctors' offices.

New methods using inert gases in multiple or single breathing provide information about ventilation heterogeneity.[29] In contrast, capnography equipment is less expensive than the equipment used in gas washout techniques and lung clearance index, because it uses an endogenous gas, making the test faster, without adjustments of gas volumes for different ages, as it is the case for gas washout tests.

Conclusion

The results show that increased slope3/VT in asthmatic patients may reflect the inhomogeneity of ventilation in distal air spaces, suggesting the presence of both chronic structural disorders of the airways and reversible acute changes observed on BPT. This index can be a useful tool in the evaluation and study of small airway dysfunction in children and adolescents with asthma.

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