

# Noninvasive ventilation and respiratory physical therapy reduce exercise-induced bronchospasm and pulmonary inflammation in children with asthma: randomized clinical trial

Maisi Muniz Cabral David, Evelim Leal de Freitas Dantas Gomes ,  
Maryjose Carvalho Mello and Dirceu Costa

## Abstract

**Background:** Asthma is characterized by hyperresponsiveness of the airways, and exercise-induced bronchospasm (EIB) is a symptom that limits a large proportion of asthmatic patients, especially children. Continuous positive airway pressure (CPAP) leads to a reduction in the reactivity of the airways. The aim of this study was to evaluate the effect of outpatient treatment with CPAP and bilevel pressure combined with respiratory physical therapy for children and adolescents with asthma following bronchial hyperresponsiveness caused by an exercise bronchoprovocation test.

**Methods:** A randomized, controlled, blind, clinical trial was conducted involving 68 asthmatic children and adolescents aged 4 to 16 years divided into three groups: G1, treated with bilevel pressure (inspiratory positive airway pressure: 12 cm H<sub>2</sub>O; expiratory positive airway pressure: 8 cm H<sub>2</sub>O), G2, treated with CPAP (8 cm H<sub>2</sub>O) and G3, treated with respiratory muscle training (RMT), considered as the control group. All groups were treated at an outpatient clinic and submitted to 10 1-hour sessions, each of which also included respiratory exercises. Evaluations were performed before and after treatment and involved spirometry, an exercise bronchoprovocation test, respiratory pressures, fraction of nitric oxide (FeNO), the Asthma Control Questionnaire (ACQ6) and anthropometric variables. This study received approval from the local ethics committee (certificate number: 1487225/2016) and is registered with ClinicalTrials [ClinicalTrials.gov identifier: NCT02939625].

**Results:** A total of 64 patients concluded the protocol; the mean age of the patients was 10 years. All were in the ideal weight range and had adequate height (z score: -2 to +2). The three groups demonstrated improved asthma control after the treatments, going from partial to complete control. A significant increase in maximal inspiratory pressure occurred in the three groups, with the greatest increase in the RMT group. A reduction in FeNO in the order of 17.4 parts per billion (effect size: 2.43) and a reduction in bronchial responsiveness on the exercise bronchoprovocation test occurred in the bilevel group. An improvement in FeNO on the order of 15.7 parts per billion (effect size: 2.46) and a reduction in bronchial responsiveness occurred in the CPAP group. No changes in lung function or responsiveness occurred in the RMT group.

**Conclusion:** Positive pressure and respiratory exercises were effective in reducing pulmonary inflammation, exercise-induced bronchoespasm (EIB), and increased the clinical control of asthma, as well as RMT, which also resulted in improved clinical control.

**Keywords:** EIB, Asthma, CPAP, Bilevel, Noninvasive ventilation, children, chest physical therapy, respiratory physical therapy, lung inflammation, asthma control

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Correspondence to:  
**Evelim Leal de Freitas  
Dantas Gomes**  
Nove de Julho University,  
São Paulo, Brazil  
[evelimfreitas@hotmail.com](mailto:evelimfreitas@hotmail.com)

**Maisi Muniz Cabral David  
Maryjose Carvalho Mello  
Dirceu Costa**  
Nove de Julho University,  
Rua Vergueiro, 235/249 -  
Liberdade, São Paulo - SP,  
Brazil 01504-000

## Introduction

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.<sup>1</sup> This condition imposes important limitations regarding activities of daily living, physical exercise and quality of life in both adults and children.<sup>2–4</sup> It is therefore essential to evaluate bronchial hyperresponsiveness for the best orientation with regard to treatment.

In the different ways to evaluate bronchial hyperresponsiveness, dynamic lung volumes are considered, such as forced expiratory volume in the first second (FEV<sub>1</sub>) and forced expiratory flow (FEF) between 25–75% following an exercise bronchial provocation (EBP) test on a treadmill.<sup>5</sup> It is estimated that 40–90% of asthmatic children develop exercise-induced bronchospasm (EIB).<sup>6</sup>

The mechanisms by which EIB develops are not yet well established, but, according to Shei and colleagues,<sup>7</sup> when an asthmatic individual performs intense physical exercise for a short period of time, an abrupt increase occurs in the amount of air to be heated and humidified by the airways, leading to a considerable loss of water that causes dehydration, with a consequent increase in the osmolarity of the fluids that line the conducting airways. This phenomenon is believed to trigger the recruitment of inflammatory cells, which leads to the release of mediators, such as histamine, leukotrienes, cysteine and prostaglandins, causing the contraction of the smooth muscles of the bronchioles and edema in these areas.<sup>6</sup>

EIB is the main cause of poor physical performance in children,<sup>8</sup> as it leads to a reduction in physical activity, thereby contributing to poorer clinical control of asthma, which, in turn, favors the aggravation of EIB, creating a cycle that is difficult to break.<sup>9</sup>

In a systematic review by Bruurs and colleagues,<sup>10</sup> physical therapy techniques, such as respiratory exercises and respiratory muscle training (RMT), demonstrated benefits with regard to reducing symptoms and the need for bronchodilators as well as increasing inspiratory muscle strength. However, little is known regarding the effects of RMT on EIB and pulmonary inflammation.

Noninvasive ventilation (VNI) has been used in the hospital setting for the treatment and control of asthma during an acute attack. Busk and colleagues<sup>2</sup> demonstrated that the administration of continuous positive airway pressure (CPAP) to stable adults led to a reduction in the responsiveness of the airways and the authors considered this nonpharmacological tool to be very important to the treatment of bronchial reactivity.

Considering the need for complementary therapy, such as physical activity, for the maintenance of the clinical control of asthma, the hypothesis tested herein is that VNI with positive pressure combined with respiratory physical therapy (RMT and respiratory exercises) in stable asthmatic children undergoing medicinal treatment can have a positive effect by reducing the triggering and intensity of EIB. Thus, the aim of the present study was to evaluate the effects of outpatient VNI (CPAP and bilevel pressure) on the responsiveness of the airways, pulmonary inflammation and the clinical control of asthma in children and adolescents.

## Material and methods

A randomized, controlled, blind, clinical trial was conducted involving treatment with VNI (CPAP or bilevel pressure) combined with respiratory exercises compared with respiratory physical therapy without positive pressure involving exercises and RMT in children and adolescents with asthma. This study received approval from the ethics committee of the Nove de Julho University (certificate number: 1487225/2016), was conducted in compliance with Resolution 466/2012 of the Brazilian National Board of Health and is registered with ClinicalTrials [ClinicalTrials.gov identifier: NCT02939625].

## Patients

Parents or guardians of children on the waiting list for the Cardiopulmonary Physical Therapy Clinic of the Nove de Julho University in São Paulo, Brazil were contacted by telephone to schedule an initial evaluation with patients who fitted the target profile in the study. During this contact, the parents/guardians received clarifications regarding the evaluations and treatment. Those who demonstrated interest scheduled a time for the initial evaluation and were instructed to ensure that the children did

not ingest beverages with caffeine or cocoa at least 12 h before the test, nor perform physical activity in the 6 h prior to the test, nor eat or ingest liquids in the 4 h prior to the test, urinate 30 min prior to the test and not to take or inhale any type of asthma control medication before the evaluation.

The following were the inclusion criteria:

- Age 4–16 years;
- Both sexes;
- Diagnosis of asthma based on the criteria of the Global Initiative for Asthma;
- In follow up with a pulmonologist and adjusted medications;
- Provided a signed statement of informed consent from both the parent/guardian and child/adolescent.

The following were the exclusion criteria:

- Having used a bronchodilator less than 12 h prior to the evaluation;
- Inability to understand or perform any of the tests due to physical or mental limitations;
- Intolerance of the proposed activities;
- Inflammatory, congenital or ischemic heart disease;
- Undergoing an infectious process with fever.

The sample size was calculated based on two previous studies involving bronchoprovocation in asthmatic adults using methacholine and treatment with CPAP. Lin and colleagues<sup>11</sup> treated 12 patients and Busk and colleagues<sup>2</sup> treated 25 patients (16 submitted to CPAP and 9 submitted to a sham procedure). In addition to considering the studies the sample was calculated from a pilot study with 15 patients, the outcomes considered in the calculation were FEV<sub>1</sub> before and after treatment and a pre- and post-bronchial provocation test. For this outcome, we considered a power of 80% with 0.05 significance, a difference to be detected of 0.2 liters and a standard deviation of 0.3, generating a sample of 20 patients per group. For the outcome for fraction of nitric oxide (FeNO), we considered a difference to be detected of 15 parts per billion (ppb) with a standard deviation of 15.3, a power of 90% of the sample and a sample of 11 patients. For the Asthma Control Questionnaire (ACQ6), the difference to be

detected was 0.5, with a standard deviation of 0.8, a power of 80% of the sample and 20 patients per group. Thus, considering the three main outcomes, the sample was 20 patients per group with a power of 80%. Overall, eight additional individuals (a total of 68 volunteers) were recruited to compensate for possible dropouts. Of these, four were unable to fulfill the commitment and the final sample comprised 64 volunteers.

### Randomization

The patients were randomly allocated to three groups. A randomized block was performed using the website, randomization.com, which generated an allocation sequence. For this, 64 evaluation charts were separated into three groups (G1, G2, G3) and placed into opaque envelopes. At the initial evaluation, the participant randomly selected an envelope stipulating the group they would belong to. The evaluator and statistician were blinded to the allocation of the participants to the different groups.

### Experimental design

The evaluations were performed on a single day and no medication was used. The patients and their guardians received clarifications regarding the procedures and evaluations and were presented with the statements of consent to be signed by the parents/guardians and children older than 7 years of age. All patients who were literate and more than 7 years old signed a consent form in addition to the consent signed by the parents/guardians. Children of 4–7 years of age who were not literate were included only with the consent form signed by their parents or guardians.

The participants in all groups participated in 10 1-hour sessions twice a week, the first 20 min of which were dedicated to respiratory exercises in the supine and sitting positions for respiratory re-education and awareness, such as diaphragm exercises, fractionated inhalation and pursed lip breathing, each with three sets of 10 repetitions.

- (a) Group 1 (G1): After 20 min of respiratory exercises, CPAP (Resmed® model S8, TM, San Diego USA) with 8 cm H<sub>2</sub>O was administered for 40 min.
- (b) Group 2 (G2): After the calculation of the 30% load for inspiratory muscle strength and after 20 min of respiratory exercises,

the protocol was initiated with the Threshold IMT<sup>®</sup> device (Respironics, Cedar Grove, NJ, USA), using a load of 30% of respiratory muscle strength for 30 min. Using the spring-load valve, which imposes adjustable inspiratory resistance, the maximal inspiratory pressure (MIP) load was increased by 10% after the first five sessions.

- (c) Group 3 (G3): After 20 min of respiratory exercises, bilevel pressure (BIPAP Respironics<sup>®</sup>) with an inspiratory positive airway pressure of 12 cm H<sub>2</sub>O and an expiratory positive airway pressure of 8 cm H<sub>2</sub>O was performed for 40 min.

The outcomes were hyperresponsiveness evaluated by the EBP test, inflammation by the exhaled nitric oxide and clinical control by the ACQ6.

## Evaluations

### *Pulmonary inflammation: FeNO*

The FeNO was determined using the criteria of the American Thoracic Society (ATS) in the sitting position with the NIOX Mino<sup>®</sup> device (Aerocrine, Aerocrine<sup>TM</sup> - Sweden). The volunteer first exhaled as much as possible to the expiratory reserve volume and then inhaled as deeply as possible through the mouth, thereby eliminating the possibility of contamination from the gas.<sup>12,13</sup> Next, exhalation was performed with a constant flow for at least 6 s. After 100 s, FeNO was quantified in ppb on the display of the device. To avoid contamination of the air from the sinus cavities, the procedure was performed with the volunteer wearing a nose clip.

### *Anthropometric variables*

Body weight was determined using a digital scale (Filizola<sup>®</sup>, Brazil). Height was determined using a wall stadiometer (Wiso, Brazil) with millimeter precision. The body mass index (BMI) was determined (kg/m<sup>2</sup>) and *z* scores were obtained using the AnthroPlus program, which employs the standards of the World Health Organization (WHO). BMI *z* scores were used to classify the children and adolescents as either in the ideal range or obese.<sup>14</sup>

### *Clinical control of asthma*

The ACQ6 was used to evaluate the clinical control of asthma among the patients. This measure is

composed of six questions referring to the previous week, five of which address symptoms of asthma and one addresses the use of a short-acting  $\beta$ 2-agonist as a rescue drug. The total score is the mean of the items and ranges from 0 (completely controlled) to 6 (uncontrolled). The cutoff point for controlled/uncontrolled asthma is 1.5 points. The following classifications were used: <0.75 = controlled; 0.75–1.5 = partially controlled; and >1.5 uncontrolled. A minimally important clinical difference on a six-point scale is 0.5.<sup>15,16</sup>

### *Respiratory muscle strength*

The evaluations of respiratory muscle strength were performed using a pressure meter (Wika<sup>®</sup>, Brazil) scaled in cm H<sub>2</sub>O equipped with an air escape valve to avoid interference from the muscles of facial mimicry. The readings were performed following the method described by Black.<sup>17</sup> The volunteer wore a nose clip and remained seated. The MIP was determined, beginning with maximal expiration and maximum expiratory pressure (MEP) was determined beginning with maximal inspiration. Each maneuver was repeated from five to eight times and the highest value was recorded, provided it did not exceed the next highest value by more than 10%.<sup>18,19</sup>

### *Lung function: spirometry*

The lung function tests were performed with a spirometer, following the criteria of the ATS.<sup>13</sup> The following volumes, capacities and flows were evaluated: forced vital capacity (FVC), FEV<sub>1</sub>, FEV<sub>1</sub>/FVC ratio and FEF between 25–75%.

The test consisted of maximal inspiratory and expiratory maneuvers performed using a previously calibrated spirometer (EasyOne<sup>®</sup>, NDD, Zurich, Switzerland) and nose clip. The patient was instructed how to perform inspiration and expiration at the adequate velocity and intensity, following the recommendations of the ATS.<sup>19</sup> All tests were performed in a climate-controlled environment. The reference values described by Polgar<sup>20</sup> were adjusted for children and used for the classification and determination of post-intervention changes.

### *EBP test*

Blood pressure, peripheral oxygen saturation (SpO<sub>2</sub>) and resting heart rate (HR) were recorded. The volunteer was then instructed to

stand on the treadmill and received instructions regarding the procedure, such as the increase in velocity and inclination of the treadmill, the use of a nose clip and mouth breathing and to communicate to the evaluator to interrupt the test if experiencing any ill feeling.

The recommendations of the ATS were followed. A load and intensity necessary to reach 80–90% maximum HR ( $208 - \text{age} \times 0.7$ )<sup>21</sup> were used. The test was performed in a climate-controlled room (temperature: 21°C; relative air humidity: 10–15%).<sup>22</sup> The target intensity was reached 2–4 min after the onset of the test and maintained for 4–6 min with the patient wearing a nose clip. During the test, HR and SpO<sub>2</sub> were monitored and the volunteer was observed for indications of intense fatigue and important changes. Immediately after the test (at approximately 6 min), the volunteer was instructed to sit in a chair and the vital signs were collected again. After approximately 5 min, the first spirometric variable was collected (post-treadmill test FEV<sub>1</sub>) to determine the occurrence of EIB, which was recorded if the reduction in this variable was equal to or greater than 10%.<sup>22</sup> FEV<sub>1</sub> was also determined at 10, 15, 20 and 25 min.

Figure 1 displays the experimental design in accordance with the Consolidated Standards Of Reporting Trials statement.

#### *Treatment of data and statistical analysis*

The Shapiro–Wilk test was used to determine the normality of the data. Parametric data were expressed as the mean and standard deviation. Nonparametric data were expressed as the median and interquartile range (25–75%). A two-way analysis of variance (ANOVA) (followed by Tukey's post-hoc test) and Friedman's test (followed by Dunn's post-hoc test) were used for the comparisons among groups. The analyses were performed using the Minitab (State College, Pensilvânia) 14 program, with the level of significance set to 5% ( $p \leq 0.05$ ). Cohen's  $d$  was used for the determination of the effect size and interpreted based on Cohen:<sup>23</sup> 0.21–0.49 = small effect size; 0.50–0.79 = medium effect size; and  $>0.80$  = large effect size.

## **Results**

A total of 68 asthmatic children were recruited, but 4 were unable to fulfill the commitment (due

to distance from the treatment site). Thus, 64 individuals aged 4–16 years concluded the treatments and evaluations.

The results of the data treatment are presented in the tables and figures below in mean, standard deviation and  $z$  scores for each group to enable inter-group and intra-group comparisons of airway inflammation, asthma control (ACQ6), lung function, respiratory muscle strength (MIP and MEP) and EIB. Table 1 displays the general baseline characteristics of the sample.

The three groups were similar and were classified in the ideal BMI range. All three groups exhibited partial asthma control and FeNO greater than 20 ppb, demonstrating a high degree of pulmonary inflammation.<sup>24</sup> Table 2 displays the results regarding the inflammation of the airways (based on the evaluation of FeNO) after the interventions.

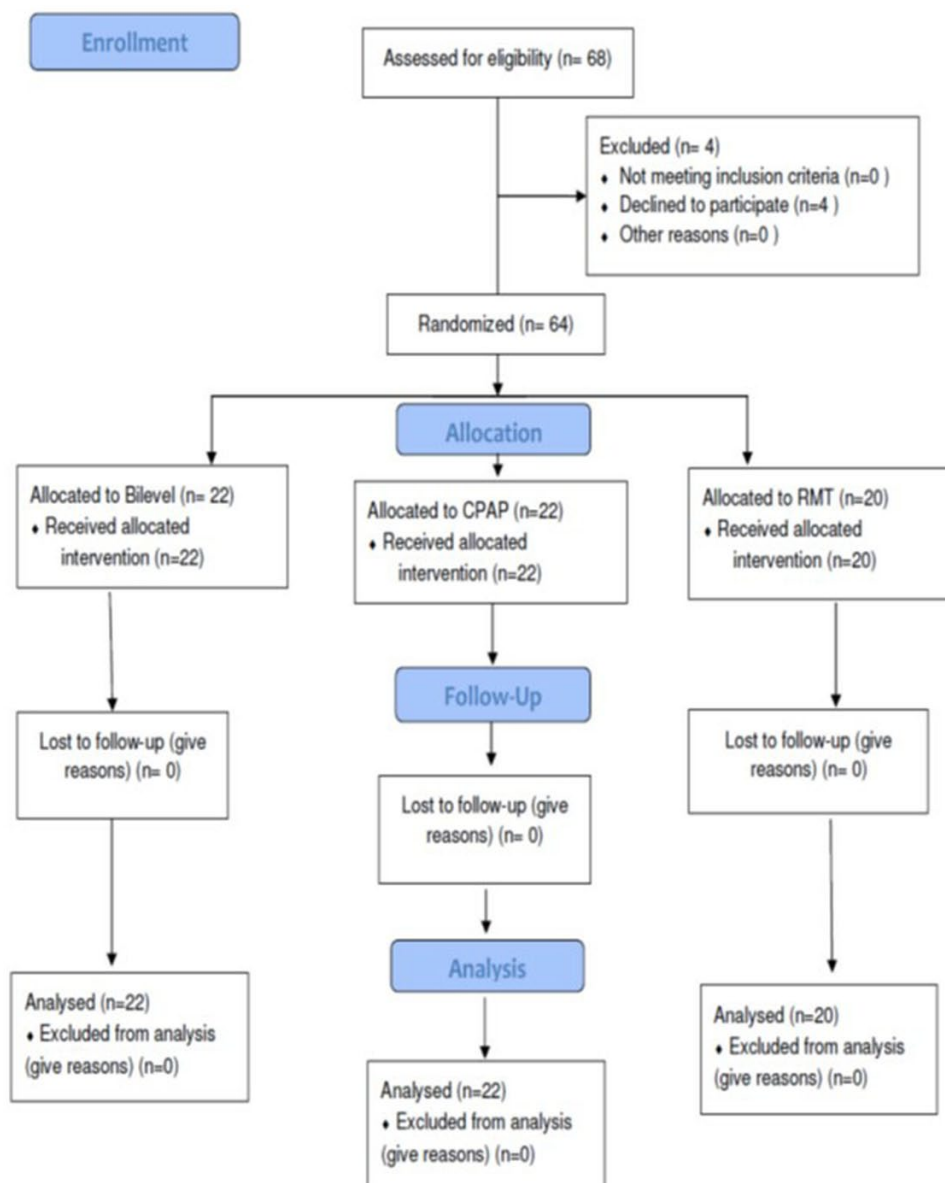
Significant reductions in FeNO occurred in the bilevel pressure and CPAP groups following the interventions, whereas no significant change occurred in the RMT group. All groups had FeNO higher than normal values (20 ppb), confirming the eosinophilic inflammatory process. Table 3 displays the results of the ACQ6 expressed in median, minimum and maximum values as well as the delta of change and effect size.

Clinically important differences between pre-intervention and post-intervention asthma control were found in all groups, with levels lower than 0.75 in the post-intervention evaluation, indicative of complete asthma control.

Table 4 displays the lung function (spirometry) results expressed in mean and standard deviation of the percentage of predicted values. No significant differences between the pre-intervention and post-intervention values were found in any of the groups.

Table 5 displays the results for respiratory muscle strength, determined as MIP and MEP and expressed as mean and standard deviation values. An increase in MIP occurred in all three groups and an increase in MEP only occurred in the RMT group. In the inter-group analysis, the MIP and MEP were significantly higher in the RMT group in comparison with the other two groups during the post-intervention intervention evaluation.





**Figure 1.** Flowchart.

CPAP, continuous positive airway pressure; RMT, respiratory muscle training.

Among the 22 patients in the bilevel pressure group, 5 had no reaction to the bronchoprovocation test, 11 exhibited mild EIB (10–24% reduction in  $FEV_1$ ), 5 exhibited moderate EIB (25–49% reduction in  $FEV_1$ ) and 1 exhibited severe EIB (>50% reduction in  $FEV_1$ ) during the pre-intervention evaluation. After treatment, 5 had no reaction, 14 exhibited mild EIB, 3 exhibited moderate EIB and no cases of severe EIB occurred. In the comparison of pre-treatment and post-treatment values (paired  $t$  test), post-bronchoprovocation  $FEV_1$  was significantly higher at

10 ( $p = 0.01$ ), 15 ( $p = 0.04$ ) and 20 min ( $p = 0.01$ ) after treatment (‡). Considering only the pre-treatment values (ANOVA), a significant reduction in  $FEV_1$  occurred at 5, 10, 15 and 20 min ( $p < 0.05$ ) post-provocation in comparison with the pre-provocation values (\*). Considering the post-treatment values (ANOVA), a significant reduction in  $FEV_1$  occurred only at 5 and 10 min ( $p < 0.05$ ) (†) (Figure 2).

Among the 20 individuals in the RMT, 6 did not react to the bronchoprovocation test, 7 exhibited

**Table 1.** General characteristics of the sample prior to treatment.

	Bilevel pressure group ( <i>n</i> = 22)	RMT group ( <i>n</i> = 20)	CPAP group ( <i>n</i> = 22)
Age (years)	10.3 ± 2.8	11 ± 3.3	9.0 ± 3.4
Height (m)	1.42 ± 0.14	1.44 ± 0.17	1.17 ± 0.17
Weight (kg)	40.4 ± 13.3	42.8 ± 12.01	37.2 ± 10.5
Sex (M/F)	9/13	8/12	11/11
Weight z score	1.51	1.45	1.48
Height z score	0.68	0.13	0.69
BMI z score	1.64	1.50	1.49
FEV <sub>1</sub> (%)	77.3 ± 16.4	80.2 ± 20.6	83.7 ± 17.3
FeNO (ppb)	52.7 ± 37.9	40.8 ± 35.6	53.5 ± 37.4
ACQ6	1.25 [0–2.8]	0.83 [0–5]	1.16 [0–3.5]

Data are expressed as mean and standard deviation.  
ACQ6, Asthma Control Questionnaire; BMI, body mass index; CPAP, continuous positive airway pressure; F, female; FeNO, fraction of exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; M, male; RMT, respiratory muscle training.

**Table 2.** Pre-intervention and post-intervention FeNO in three groups.

	Bilevel pressure group ( <i>n</i> = 22)		RMT group ( <i>n</i> = 20)		CPAP group ( <i>n</i> = 22)	
	Pre	Post	Pre	Post	Pre	Post
FeNO	52.7 ± 37.9	35.3 ± 15.3*	40.8 ± 35.6	35.9 ± 25.2	53.5 ± 37.4	37.7 ± 26.1*
Δ FeNO	17.4†		4.9		15.7†	
Effect Size	2.43				2.46	

\*significant intra-group difference: pre versus post-intervention ( $p \leq 0.05$ );  
†significant intra-group difference ( $p \leq 0.05$ ); effect size calculated based on Cohen.<sup>23</sup>  
CPAP, continuous positive airway pressure; FeNO, fraction of exhaled nitric oxide; RMT, respiratory muscle training.

mild EIB, 6 exhibited moderate EIB and 1 exhibited severe EIB prior to treatment. After treatment, eight did not react to the test, five exhibited mild EIB, five exhibited moderate EIB and two exhibited severe EIB. An ANOVA for the comparison of pre-treatment values revealed a significant reduction in FEV<sub>1</sub> at 5 and 10 min ( $p < 0.05$ ) post-bronchoprovocation in comparison with pre-test values. At the post-intervention evaluation, no significant difference in FEV<sub>1</sub> values were found, which continued to be lower at 5 and 10 min.

Among the 22 individuals in the CPAP group, 5 did not react to the bronchoprovocation test, 9 exhibited mild EIB, 6 exhibited moderate EIB and 2 exhibited severe EIB during the pre-intervention evaluation. After treatment, six did not react to the test, eight exhibited mild EIB, seven exhibited moderate EIB and one exhibited severe EIB. An ANOVA for the comparison of pre-treatment values revealed a significant reduction in FEV<sub>1</sub> at 5 and 10 min (\*) ( $p < 0.05$ ) post-bronchoprovocation in comparison with pre-test

**Table 3.** Pre-intervention and post-intervention asthma control in three groups.

	Bilevel pressure group (n = 22)		RMT group (n = 20)		CPAP group (n = 22)	
	Pre	Post	Pre	Post	Pre	Post
ACQ6	1.25 [0–2.8]	0.58 [0–2]	0.83 [0–5]	0.33 [0–3]	1.16 [0–3.5]	0.66 [0–2.5]
Δ ACQ6	0.67***		0.5***		0.5***	
Effect size	2.4		0.3		0.9	

\*\*\*clinically important difference; ACQ6 expressed in median, minimum and maximum values.  
ACQ6, Asthma Control Questionnaire; CPAP, continuous positive airway pressure; RMT, respiratory muscle training.

**Table 4.** Pre-intervention and post-intervention lung function in three groups.

	Bilevel pressure group (n = 22)		RMT group (n = 20)		CPAP group (n = 22)	
	Pre	Post	Pre	Post	Pre	Post
FVC %	90.7 ± 11.9	92.5 ± 12.5	92.7 ± 16.9	95.1 ± 13.5	98.4 ± 14.1	97.8 ± 13.5
FEV <sub>1</sub> %	77.3 ± 16.4	80.5 ± 17.5	80.2 ± 20.6	82.2 ± 16.4	83.7 ± 17.3	81.5 ± 15.7
FEV <sub>1</sub> /FVC%	82.3 ± 8.8	86.8 ± 8.9	85.3 ± 85.2	85.2 ± 11.9	85.0 ± 11.06	83.8 ± 10.6
FEF 25–75%	60.63 ± 23.7	72.9 ± 24.4	71.2 ± 25.2	67.9 ± 26.1	72.4 ± 27.8	68.3 ± 23.2

CPAP, continuous positive airway pressure; FEF, forced expiratory flow; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RMT, respiratory muscle training.

**Table 5.** Pre-intervention and post-intervention respiratory muscle strength (MIP and MEP) in three groups.

	Bilevel pressure group (n = 22)		RMT group (n = 20)		CPAP group (n = 22)	
	Pre	Post	Pre	Post	Pre	Post
MIP	48.1 ± 22.1	56.3 ± 17.8*	55.5 ± 84.5	84.5 ± 29.6*†	52.5 ± 30.5	59.7 ± 26.2*
MEP	50 ± 22.6	56.8 ± 15.5	53.5 ± 16.9	73.5 ± 27.1*†	46.13 ± 18.12	52.04 ± 22.0

\*significant intra-group difference: pre versus post-intervention ( $p \leq 0.05$ );  
†significant intra-group difference ( $p \leq 0.05$ ).  
CPAP, continuous positive airway pressure; MEP, maximum expiratory pressure; MIP, maximal inspiratory pressure; RMT, respiratory muscle training.

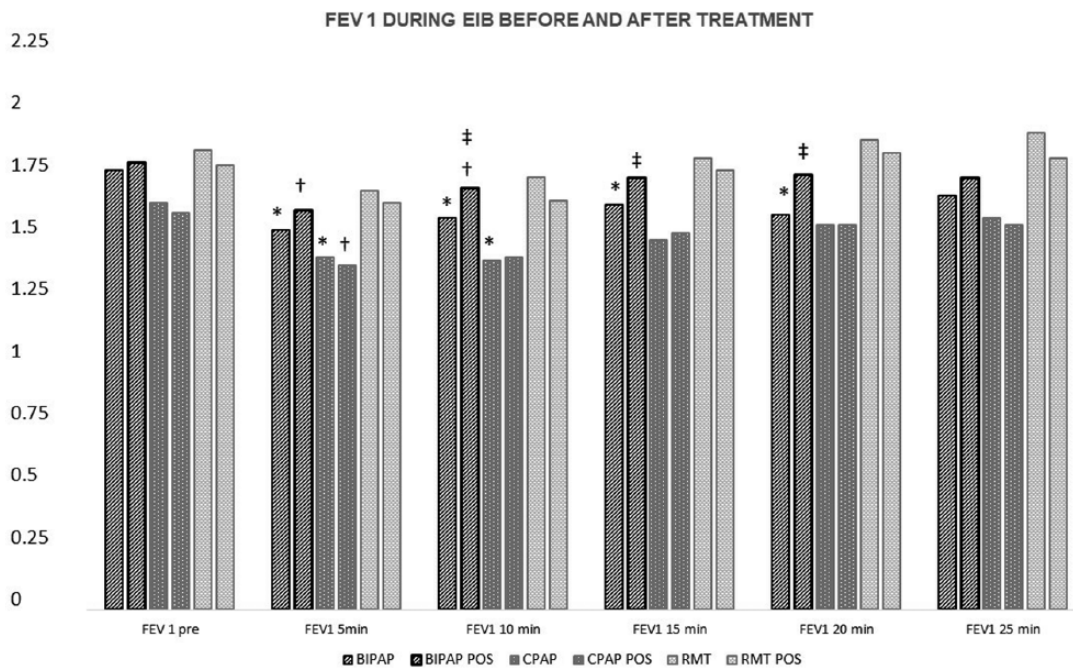
values. After treatment, a significant difference in FEV<sub>1</sub> was only found at 5 min (†) ( $p < 0.05$ ).

### Discussion

Based on the presented results, treatment with CPAP and bilevel pressure led to reductions in

the severity of EIB in children and adolescents with asthma. This finding is in agreement with data described by Busk and colleagues<sup>2</sup> who consider CPAP to be an important nonpharmacological tool for the treatment of asthma, as it reduces the bronchial reaction to methacholine in asthmatic adults.





**Figure 2.** Pre-treatment and post-treatment FEV<sub>1</sub> in three groups. BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; EIB, exercise-induced bronchospasm; FEV<sub>1</sub>, forced expiratory volume in 1 second; POS, post intervention; RMT, respiratory muscle training.

The results were similar in the CPAP and bilevel pressure groups with regard to reactivity and the severity of EIB. This is an important finding, as the present investigation is the first study to explore two positive pressure therapeutic methods on the airways of asthmatic patients, specifically stable children and adolescents. As expected, no changes were observed in the severity of EIB that occurred in the RMT group.

Regarding pulmonary inflammation, significant reductions in FeNO were found in both the CPAP and bilevel pressure groups, further underscoring the effectiveness of these positive pressure methods for individuals with asthma. This finding has a physiological basis. The stretching mechanism of the airways stimulates the production of neuronal NO by the activation of the inhibitory non-adrenergic non-cholinergic (NANC) pathway, leading to a reduction in the effect of induced NO, 'interrupting' the inflammatory cycle in the airways<sup>25</sup> and ultimately leading to bronchodilation and a reduction in inflammation.<sup>26</sup>

While improvements were found in both groups submitted to positive pressure in the airways, the fact that the bilevel pressure group demonstrated better results with regard to both reactivity and

inflammation may be explained by the addition of inspiratory pressure, which promotes greater stretching of the airways, thereby potentiating the neural effect on the smooth muscles.<sup>11</sup>

A curious and important finding was the increase in MIP in all three groups analyzed. While this result was expected in the RMT group, it was not expected in the groups subjected to positive pressure. The explanation for this may reside in the fact that, independently of RMT, the pressures imposed on the airways may have led to a reduction in lung hyperinflation, thereby potentiating the action of the inspiratory muscles. According to Shei and colleagues,<sup>7</sup> lung hyperinflation, which leads to an increase in final expiratory volume, is a characteristic of asthma that occurs due to the premature closing of small-caliber airways, increasing the activity of the respiratory muscles at the end of exhalation. According to Silva and colleagues,<sup>27</sup> lung hyperinflation likely contributes to the symptoms related to asthma, with the compression of the diaphragm and assessor inspiratory muscles, forcing this musculature to work further from its ideal curvature to perform adequate contraction, which leads to the distortion of the diaphragm and horizontal tractioning of the ribs, causing the flattening of the dome and

a reduction in inspiratory capacity.<sup>28</sup> Therefore, the increase in inspiratory muscle strength in the bilevel pressure and CPAP groups in the present study likely occurred because the respiratory mechanics of the patients was favored and a reduction in respiratory work occurred when positive pressure was applied in the airways.

The present results underscore the importance of nonpharmacological therapy as a complement to drug therapy as well as the importance of follow up on the part of the physiotherapist when asthma patients are in the stable phase. In the present study, clinical control (as represented by the ACQ6) was achieved in all three study groups, which included respiratory exercises. This results offer a scientific basis for the physiotherapeutic treatment of asthmatic patients.

Regarding EIB, indirectly provoked hyperresponsiveness using physical exercise is less sensitive, but more specific than the response induced using methacholine.<sup>29</sup> In the bilevel pressure group, the reduction in FEV<sub>1</sub> appeared from the 5th to the 20th minute post-bronchoprovocation at the pre-intervention evaluation, but only from the 5th to 10th minute at the post-intervention evaluation.

The severity of EIB has been explored and demonstrated by Parsons and colleagues.<sup>22</sup> Among the patients in the bilevel pressure group in the present investigation, 5 had no reaction to the bronchoprovocation test, 11 exhibited mild EIB (10–24% reduction in FEV<sub>1</sub>), 5 exhibited moderate EIB (25–49% reduction in FEV<sub>1</sub>) and 1 exhibited severe EIB (>50% reduction in FEV<sub>1</sub>) during the pre-intervention evaluation. After treatment, 5 had no reaction, 14 exhibited mild EIB, 3 exhibited moderate EIB and no cases of severe EIB occurred. These findings demonstrate that this positive pressure method reduced bronchial hyperresponsiveness in the children/adolescents with asthma.<sup>2,11</sup>

RMT combined with respiratory exercises assists in the clinical control of asthma. The literature also reports reductions in dyspnea and hyperventilation, lending further support to the importance of combining these methods, although these aspects were not evaluated in the present investigation.

The main limitation of the present study was that the improvement in EIB was explained by physiology, since it is impossible to perform a direct

measure of this variable in humans. This study contributes a new way to use VNI outside the hospital environment to optimize outpatient physical therapy for patients with asthma.

### Conclusions

Based on the findings of the present study, positive pressure therapy is effective at reducing EIB and pulmonary inflammation in children and adolescents, thereby enabling better clinical control of asthma. The reduction in the inflammatory process of the airways and improved clinical control demonstrate the relevance of VNI in this population in periods of stability, which could also lead to an improvement in quality of life due to the reduction in the symptoms and limitations imposed by asthma. RMT and respiratory exercise led to clinical control and reduced inflammation to a lesser degree, and must be used for these patients. Further studies with a longitudinal design are needed for a better follow up of this population in the growth and physical development phase of life.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

### ORCID iD

Evelim Leal de Freitas Dantas Gomes  <https://orcid.org/0000-0002-0636-6041>

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