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Title: Ventilation rates achieved in eucapnic voluntary hyperpnea challenge and exercise-induced bronchoconstriction diagnosis in young patients with asthma

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Abstract

Purpose: Exercise-induced bronchoconstriction (EIB) affects approximately 50% of young asthma patients, impairing their participation in sports and physical activities. Eucapnic voluntary hyperpnea (EVH) is an approved surrogate challenge to exercise for objective EIB diagnosis, but the required minimum target hyperventilation rates remain unexplored in this population. This study aimed to evaluate the association between the achieved ventilation rates (VRs) during a challenge and EIB-compatible response (EIB-cr) in young asthma patients. **Methods:** This cross-sectional study included 72 asthma patients aged 10–20 years. Forced expiratory volume in the first second (FEV1) was measured before and 5, 15, and 30 min after the EVH. The target VR was set at 21 times the individual's baseline FEV1. A decrease of >10% in FEV1 after the challenge was considered an EIB-cr. The challenge was repeated after 48–72h in those without an EIB-cr. **Results:** Thirty-six individuals had an EIB-cr at initial evaluation. The median VRs achieved was not different between individuals with and without an EIB-cr (19.8 versus 17.9; p=0.619). The proportion of individuals with an EIB-cr was nor different comparing those who achieved (12/25) or not (24/47) the calculated target VRs (p=0.804). At the repeated EVH challenge an EIB-cr was observed in 14/36 individuals with a negative response in the first evaluation, with no differences in achieved VRs between the two tests (p=0.463). Conclusion: Irrespective of the achieved VR, an EIB compatible response after an EVH challenge must be considered relevant for clinical and therapeutic judgment, and negative tests should be repeated.

Keywords: Exercise-induced bronchoconstriction, Lung function, Asthma, Eucapnic voluntary hyperpnea.

Introduction

Approximately 33–59% of asthma patients report exercise-associated respiratory symptoms[1]. These symptoms may restrict their participation in salutary peer group physical activities, sports, and games[2–4]. Exercise-induced bronchoconstriction (EIB) is the most common, although not the only cause of these symptoms[5,6], and affects approximately 50% of young asthma patients[5], 10% of youngsters without asthma[6], and a significant proportion of competitive athletes[7]. EIB is defined as acute narrowing of the lower respiratory airways after exercise[5]. Correct EIB diagnosis is important to ensure effectiveness of the treatment and to overcome the limitations of participation in sports and physical activities or playing, thereby promoting a healthy lifestyle[8].

Symptoms alone do not allow for an accurate diagnosis of EIB, and standardized objective tests are required[9–11]. The most common challenge/test conducted for detecting EIB in clinical practice is running on a treadmill or pedaling on a stationary bicycle. This involves increasing the exercise intensity in the first 2 min to achieve a heart rate between 80% and 90% of the predicted maximum, and maintaining this exercise intensity for another 4–6 min[5]. This protocol requires baseline and serial measurements of the forced expiratory volume in the first second (FEV_1) for 30-min after the exercise. EIB diagnosis is established if there is a reduction in the FEV_1 of $\geq$10% as compared to the baseline value at any moment after the challenge[5]. Some individuals may not be able to complete these challenges, or achieving the target heart rates may be difficult in highly trained athletes[12].

The main determinants of EIB are dehydration and thermal stress imposed on the airway epithelium due to high ventilation rates (VRs) achieved during moderate to intense exercise. This results in water loss and osmotic changes in the periciliary fluid of the bronchial epithelium, resulting in the release of chemical mediators from the epithelial and inflammatory cells and sensory nerve activation, which leads to bronchial constriction[5, 7].

Surrogate tests for EIB diagnosis that do not require exercise and impose a similar osmotic stress on the airway epithelium include eucapnic voluntary hyperpnoea (EVH) and inhalation of saline hyperosmolar aerosols or dry powder mannitol[5]. EVH is the most studied method, is considered safe[13–15], and allows better control over ventilation and inspired air conditions[5]. In an EVH test, the patient hyperventilates for 6 min breathing in dry air enriched with 5% CO_2 (to avoid alkalosis) at a recommended VR of 21 times the individual's FEV_1 for non-athletes and 30 times the FEV_1 for athletes, corresponding to 60% and 85% of maximum voluntary ventilation (MVV), respectively[13,16].

Most studies that evaluated the influence of VR in EVH tests for EIB diagnosis were performed in athletes[12,17,18]. In a study evaluating the utility of EVH in clinical settings, the need for further investigations to explore the ventilatory stimulus threshold for EIB diagnosis became evident[14]. Therefore, the objective of this study was to verify whether FEV_1 responses indicative of an EIB diagnosis are related to the VRs achieved during EVH test in children and adolescents with asthma. We hypothesized that the higher the VR achieved, higher is the likelihood of a response indicating an EIB diagnosis.

Methods

Study design, period, and ethics

This cross-sectional study was conducted at the Pulmonary Functional Laboratory of the Hospital das Clínicas at the Federal University of Pernambuco, Recife, Brazil between March and October 2019. It was approved by the institution's Ethics Committee (Agreement No.:2.796.049). All parents and adolescents signed an informed consent form, as requested by the Brazilian Regulatory Agency.

Study population

The study participants included children and adolescents of both sexes and aged 10–20 years, having asthma. Participants who were diagnosed with asthma according to the Global Initiative for Asthma, 2018[19] were referred from the allergy and clinical immunology, pulmonology, and pediatric clinics of the same hospital to participate in the study. This hospital mainly serves the underprivileged population. Patients were first-time incomers, were in the initial clinical evaluation process and still have not had treatment readjustments to achieve adequate control of symptoms.

The exclusion criteria were as follows: baseline FEV_1<60% of the predicted value, inability to perform forced expiratory maneuvers adequately for FEV_1 determination, presence of other conditions precluding hyperpnea maneuvers required by the protocol, inability to suspend medication for the tests, use of systemic corticosteroids, or affirmative response to a question regarding the presence of respiratory infection symptoms in the 6 weeks prior to the evaluation.

Procedures

The weight(kg) and height(cm) of the participants were measured on a calibrated scale and stadiometer, respectively (Welmy W 200, Santa Barbara d'Oeste, SP, Brazil). After anthropometric measurements patients responded to the Asthma Control Test(ACT)[20].

The EVH test followed a standardized protocol [5] and was performed in the morning. Patients were instructed not to drink beverages with caffeine or perform vigorous exercise on the testing day. The duration of suspension of the medications in use was as follows: inhaled short-acting beta-2 agonists, 12 h; inhaled long-acting beta-2 agonists, 48 h; and inhaled steroids, 24 h[5].

The baseline FEV_1 was determined using a daily calibrated spirometer(microQuark, COSMED, Rome, Italy) in accordance with international protocols[21]. The measurement was repeated in duplicate at 5, 15, and 30 min after EVH, and the best FEV_1 value was selected for analysis. The predicted values were as proposed by Pereira et al.[22] for Brazilians.

For EVH, the patients breathed a mixture of dry air and 5% CO_2(White-Martins, Recife, PE, Brazil) through their mouth using a one-way low-resistance valve(Laerdal, Copenhagen, Denmark) via a Douglas balloon reservoir with a nose clip worn throughout the procedure. The test lasted 6 min, and the patients were encouraged every 30 s to reach and maintain a target VR 21 times that of their baseline FEV_1. The VR was monitored using an analogic ventilometer(Wright Mark 8 NSPIRE Health, Colorado, USA) and assessed at the end of each minute of the hyperpnea maneuver.

A decrease of ≥10% in the FEV_1 as compared to the baseline value during any measurement time point after the challenge(5, 15, or 30 min) was considered a positive response to the EVH challenge and an EIB-compatible diagnosis[5]. All negative responses were reevaluated within 48–72 h by following the same methodology and at the same hour of the day as that of the first evaluation.

Statistical analysis

The data were processed and analyzed using the Statistical Package for the Social Sciences(SPSS), version 20 and the figures were made by the GraphPad Instat program. The

Shapiro–Wilk test was applied to assess normality. Values are expressed as frequencies(%), means±standard deviations, or medians(25–75% percentile). Comparisons between the means were performed using the parametric student's t-test, while that between the medians were performed using the Mann–Whitney and Kruskal-Wallis tests. The chi-square test was used to assess differences between proportions. The Wilcoxon test was used to compare within-subjects' differences between different days. Spearman's correlation was performed to assess the relationship between the achieved VR as a multiple of the baseline FEV_1 and the maximum change in the FEV_1 expressed as a percentage change from the baseline after the EVH challenge.

The achieved VRs were classified as follows: low($\leq$17 times the baseline FEV_1), intermediate(>17 and $\leq$21 times the baseline FEV_1), and high(>21 times the baseline FEV_1). All conclusions were based on a significance level of 5%.

Results

This study included 72 young asthma patients (33 boys and 39 girls), with a mean age of 14.52±3.45 years. None of them engaged in regular sports activities. A positive FEV_1 response, i.e., decrease of ≥10% as compared to the baseline value, was noted in 36 patients (50%) after the first EVH challenge. The patients' baseline characteristics for the whole sample and categorized according to the EVH challenge responses are shown in Table 1. As shown, none of the variables, except for the FEV_1 response to the EVH, showed statistically significant differences between the categories.

Overall, the median VR achieved was 46.03 L/min (interquartile range [IQR], 38.23–64.33), which represented a median of 19.28 times the baseline FEV_1 (IQR, 16.91–22.60). The achieved VRs did not differ between individuals with and without a positive FEV_1 response to the EVH challenge, neither as a percentage of the calculated value nor as a multiple of the baseline FEV_1 (Figure 1A and B). Additionally, there was no association between the number of individuals with a positive response and the categorized VR as a multiple of the baseline FEV_1 (Table 2, top row).

Moreover, no correlation was found between the maximum FEV_1 decrease after EVH and the achieved VR as a multiple of the baseline FEV_1 (Figure 2). Even when categorizing FEV1 responses in those individuals with a reduction <10%, > 10% < 25% and those > 25% there were no differences in ventilation rates between categories (Kruskal-Wallis test; p-value = 0.888).

On the day of the second EVH challenge conducted for those with a negative EIB-compatible response (EIB-cr) in the first challenge (n=36), 14 showed a positive FEV_1 response compatible with EIB diagnosis. There were no differences in the baseline FEV_1 as a percentage of the predicted values between those with and without a positive response (median: 96.71% and 93.20% and IQR: 88.91–103.95% and 79.75–103.32%, respectively;

p=0.997). Furthermore, in the second evaluation, no association was found between the achieved VR categories and bronchial response to the EVH challenge (Table 2, bottom).

Discussion

We hypothesized that the higher the VR achieved in the EVH challenge, higher is the likelihood of an EIB-cr of FEV_1. However, our results found no association or correlation between these variables. Moreover, patients with VRs considered low (<17 times the baseline FEV_1) and those with rates considered high (>21 times the baseline FEV_1) had a similar proportion of EIB-cr. Additionally, important variations in the achieved VRs were observed even when the patients were encouraged every 30 s during the EVH challenge to attain the guideline target[5].

EVH is considered a valid surrogate to exercise challenges for EIB diagnosis[5], despite the fact that a recent meta-analysis found high agreement between the two challenges only among those individuals with negative results (using EVH as reference)[23]. Increased VR together with the inhalation of dry air during the EVH challenge simulates the stimulus of high-intensity exercise and induces dehydration and osmotic changes in the periciliary fluid layer of the bronchial mucosa[5]. This stimulates the epithelial and inflammatory cells and nerve fibers to release mediators capable of inducing a bronchospastic response[7]. For elite athletes or those who train at high VRs on a daily basis, guidelines suggest a VR of 85% of the MVV(calculated as 30 times the baseline FEV_1)[5] for an EVH challenge to be considered adequate. For asthma patients, the adequate VR is required to be at least 17.5 times the baseline FEV_1 and preferably >21 times the FEV_1 for a test to be considered valid[5].

Overall, we observed an EIB-cr in 69% of our patients: in 36 (50%) patients after the first EVH challenge and in 14 (19%) patients after the challenge was repeated within 48–72 h for those without an EIB-cr in the first evaluation. A VR <17 times the baseline FEV_1 (approximately 50% of the MVV) was achieved by 18 (25%) patients, and an EIB-cr was observed in 9 of them. In the second challenge repeated for the 36 individuals with a negative response in the initial evaluation, this low VR was achieved by 8, of which 2 showed an EIB-cr.

Another study also reported a similar rate of positive response in FEV_1 after repeating the EVH challenge in individuals who initially presented negative responses[24]. Comparable results were observed in adult recreational athletes by Price et al.[18]. They reported a positive response in the second EVH challenge in 19% of individuals who had a negative response in the first challenge. They highlighted the need for caution when excluding an EIB diagnosis based on a single EVH test presenting a negative result. Anderson et al.[25] found that 17% of their participants with a negative response in the first exercise test on a treadmill presented a positive response in the second one. Thus, excluding an EIB diagnosis based on a single EVH or exercise test should be done so cautiously.

Our study population comprised patients with an asthma diagnosis visiting a specialized clinical practice, i.e., a group in whom exercise-associated respiratory symptoms are prevalent, and EIB must be correctly diagnosed in order to provide adequate treatment[1, 8]. For the baseline characteristics that could interfere with bronchial response[5] to the EVH test, no statistical differences were observed in the percentage of predicted baseline FEV_1 and asthma control evaluated by the ACT between individuals with and without an EIB-cr.

Notably, there were no safety issues reported, and no test had to be interrupted due to respiratory symptoms or hemoglobin desaturation <94%; however, it is mandatory that the test be conducted by trained personnel and that resources be available for a possible severe response. Our experience[11] and that of others[14,15,26,27] indicate that 60% of the predicted FEV_1 value instead of 75%[5] is adequate as a safety cutoff point to conduct such challenges/tests for EIB diagnosis.

Minute ventilation, duration, and intensity of exercise are reported as the most important factors triggering EIB[5,7,13]. Although heart rate is used as a surrogate measure of the exercise intensity for diagnosing EIB, its relationship with VR varies widely based on physical fitness and other factors[13,17,18,28,29]. Similar to the findings of other authors[13,17,18,28–30], we observed an EIB-cr in many individuals who did not achieve the calculated target VR of 21 times the baseline FEV_1.

Brummel et al.[14] conducted a retrospective study on an older population that included elite and non-elite athletes and an undefined number of individuals with asthma. They reported that the proportion of EIB-cr in individuals not reaching the target VR of 21 times the baseline FEV_1 was significantly higher than that of individuals who achieved or surpassed the target VR (33% vs. 26%). In contrast to the findings of these authors, we cannot regard one negative test as sufficient to rule out an EIB diagnosis, based on the premise that an achieved VR target of ≥21 times the baseline FEV_1 is a valid EVH challenge. In fact, 39% of our patients with a negative response in the first test (14/36) showed a positive response in the second EVH challenge performed after 48–72 h, with an achieved VR below this target in half of them.

This study has some limitations. First, we did not evaluate the VR based on a maximum effort test(i.e., VR 30 times the baseline FEV_1), although the suggested VR target for asthma patients is 21 times the baseline FEV_1[5]. Second, the method of measuring the VR every minute using an analogical ventilometer instead of a continuous measurement may also have contributed to the number of individuals with a VR below the target. Third, our established target of 21 times the baseline FEV_1 may have contributed to a low number of individuals reaching this target (35%), and aiming for a higher rate(i.e., 25 or 30 times the baseline FEV_1) could have increased the achieved VR. Nevertheless, the proportion of individuals with an EIB-cr in the EVH challenge was similar to the reported literature prevalence of EIB among asthma patients(approximately 50%)[5].

In conclusion, the achieved VRs in this study did not differ between individuals with and without an EIB-cr in the EVH challenge. This indicates that VR is not the only determinant of the bronchospastic response and that other non-recognized variables may influence this process. These findings emphasize the need for further investigations to assess if there is a minimum VR and to determine that VR. Furthermore, future studies should be conducted to determine the necessary criteria to consider a test as effective and valid for EIB diagnosis. Currently, it appears that the EVH challenge should be repeated at least once in individuals without an EIB-cr in the first evaluation to rule out EIB diagnosis. Irrespective of the achieved VR, a positive FEV_1 response after EVH is suggestive of an EIB diagnosis and must be considered relevant for clinical and therapeutic assessments.

Conflict of Interest: None

References

1. Rabe KF, Adachi M, Lai CK., et al (2004) Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. J Allergy Clin Immunol 114:40–47. https://doi.org/10.1016/j.jaci.2004.04.042

2. Mancuso CA, Sayles W, Robbins L, et al (2006) Barriers and Facilitators to Healthy Physical Activity in Asthma Patients. J Asthma 43:137–143. https://doi.org/10.1080/02770900500498584

3. Velsor-Friedrich B, Vlasses F, Moberley J, Coover L (2004) Talking With Teens About Asthma Management. J Sch Nurs 20:140–148. https://doi.org/10.1177/10598405040200030401

4. Williams B, Powell A, Hoskins G, Neville R (2008) Exploring and explaining low participation in physical activity among children and young people with asthma: a review. BMC Fam Pr 9:40. https://doi.org/10.1186/1471-2296-9-40

5. Parsons JP, Hallstrand TS, Mastronarde JG, et al (2013) An official American thoracic society clinical practice guideline: Exercise-induced bronchoconstriction. Am J Respir Crit Care Med 187:1016-1027 online supplement. https://doi.org/10.1164/rccm.201303-0437ST

6. Gotshall RW (2002) Exercise-Induced Bronchoconstriction. Drugs 62:1725–1739. https://doi.org/10.2165/00003495-200262120-00003

7. Weiler JM, Anderson SD, Randolph C, et al (2010) Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. Ann Allergy Asthma Immunol 105:S1–S47. https://doi.org/10.1016/j.anai.2010.09.021

8. Lang JE (2019) The impact of exercise on asthma. Curr Opin Allergy Clin Immunol

19:118–125. https://doi.org/10.1097/ACI.0000000000000510

9. Parsons JP, Kaeding C, Phillips G, et al (2007) Prevalence of Exercise-Induced Bronchospasm in a Cohort of Varsity College Athletes. Med Sci Sport Exerc 39:1487–1492. https://doi.org/10.1249/mss.0b013e3180986e45

10. Hallstrand TS, Curtis JR, Koepsell TD, et al (2002) Effectiveness of screening examinations to detect unrecognized exercise-induced bronchoconstriction. J Pediatr 141:343–349. https://doi.org/10.1067/mpd.2002.125729

11. Dantas FMNA, Correia MAV, Silva AR, et al (2014) Mothers impose physical activity restrictions on their asthmatic children and adolescents: An analytical cross-sectional study. BMC Public Health 14:1–7. https://doi.org/10.1186/1471-2458-14-287

12. Parsons JP, Cosmar D, Phillips G, et al (2012) Screening for exercise-induced bronchoconstriction in college athletes. J Asthma 49:153–157. https://doi.org/10.3109/02770903.2011.652329

13. Anderson SD, Argyros GJ, Magnussen H, Holzer K (2001) Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction. Br J Sport Med 35:344–347. https://doi.org/10.1136/bjsm.35.5.344

14. Brummel NE, Mastronarde JG, Rittinger D, et al (2009) The clinical utility of eucapnic voluntary hyperventilation testing for the diagnosis of exercise-induced bronchospasm. J Asthma 46:683–686. https://doi.org/10.1080/02770900902972178

15. Burman J, Elenius V, Lukkarinen H, et al (2020) Cut- off values to evaluate exercise- induced asthma in eucapnic voluntary hyperventilation test for children. Clin Physiol Funct Imaging 40:343–350. https://doi.org/10.1111/cpf.12647

16. Hallstrand TS, Leuppi JD, Joos G, et al (2018) ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge

testing. Eur Respir J 52:1801033. https://doi.org/10.1183/13993003.01033-2018

17. Hull JH, Ansley L, Price OJ, et al (2016) Eucapnic Voluntary Hyperpnea: Gold Standard for Diagnosing Exercise-Induced Bronchoconstriction in Athletes? Sport Med 46:1083–1093. https://doi.org/10.1007/s40279-016-0491-3

18. Price OJ, Ansley L, Hull JH (2015) Diagnosing Exercise-Induced Bronchoconstriction With Eucapnic Voluntary Hyperpnea: Is One Test Enough? J Allergy Clin Immunol Pr 3:243–249. https://doi.org/10.1016/j.jaip.2014.10.012

19. GINA (2018) Global Initiative for Asthma (GINA). [Cited 2021 fev 11]. Available from: http://www.ginasthma.org

20. Roxo JPF, Ponte EV, Ramos DCB, et al (2010) Validação do Teste de Controle da Asma em português para uso no Brasil: validation for use in Brazil. J Bras Pneumol 36:159–166. https://doi.org/10.1590/S1806-37132010000200002

21. Miller MR (2005) Standardisation of spirometry. Eur Respir J 26:319–338. https://doi.org/10.1183/09031936.05.00034805

22. Pereira C (2002) Espirometria. J Pneumol 28:S1–S82

23. Iftikhar IH, Greer M, Jaiteh A (2019) A Meta-analysis of Diagnostic Test Agreement Between Eucapnic Voluntary Hyperventilation and Cardiopulmonary Exercise Tests for Exercise-Induced Bronchoconstriction. Lung 197:483–492. https://doi.org/10.1007/s00408-019-00233-4

24. Rizzo JÂ, Rodrigues Filho E de A, Gonçalves AV, et al (2021) Reproducibility of eucapnic voluntary hyperpnoea for exercise- induced bronchoconstriction diagnosis in asthmatic children and adolescents. Pediatr Allergy Immunol 00:1–9. https://doi.org/10.1111/pai.13610

25. Anderson SD, Pearlman DS, Rundell KW, et al (2010) Reproducibility of the airway

response to an exercise protocol standardized for intensity, duration, and inspired air conditions, in subjects with symptoms suggestive of asthma. Respir Res 11:120. https://doi.org/10.1186/1465-9921-11-120

26. Nicolai T, Mutius E V., Reitmeir P, Wjst M (1993) Reactivity to Cold-Air Hyperventilation in Normal and in Asthmatic Children in a Survey of 5,697 Schoolchildren in Southern Bavaria. Am Rev Respir Dis 147:565–572. https://doi.org/10.1164/ajrccm/147.3.565

27. Argyros GJ, Roach JM, Hurwitz KM, et al (1996) Eucapnic Voluntary Hyperventilation as a Bronchoprovocation Technique. Chest 109:1520–1524. https://doi.org/10.1378/chest.109.6.1520

28. Spiering BA, Judelson DA, Rundell KW (2004) An evaluation of standardizing target ventilation for eucapnic voluntary hyperventilation using FEV1. J Asthma 41:745–749. https://doi.org/10.1081/JAS-200028004

29. Blackie SP, Fairbarn MS, McElvaney NG, et al (1991) Normal values and ranges for ventilation and breathing pattern at maximal exercise. Chest 100:136–142. https://doi.org/10.1378/chest.100.1.136

30. Williams NC, Johnson MA, Hunter KA, Sharpe GR (2015) Reproducibility of the bronchoconstrictive response to eucapnic voluntary hyperpnoea. Resp Med 109:1262–1267. https://doi.org/10.1016/j.rmed.2015.08.006

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Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date. 2019/No.: 2.796.049).

Consent to participate: All parents and adolescents signed an informed consent form

Figure legends

Figure 1. Comparison of the achieved ventilation rates between individuals with and without positive responses on FEV_1 in the first eucapnic voluntary hyperpnea challenge. The achieved ventilation rates are expressed either as percentage of the calculated (A – Median; interquartile range: 94.26%; 76.40%–102.70% vs. 85.23%; 80.35%–106.4%), or as a multiple of baseline FEV_1 (B- Median; interquartile range: 19.79; 16.04–21.58 vs. 17.90; 16.87–22.35). (Mann–Whitney U-test). FEV_1 = forced expiratory volume in the first second.

Figure 2. Correlation between the maximum decrease in the FEV_1 after EVH and the achieved ventilation rate calculated as a multiple of the baseline FEV_1 value. Solid non-graduated horizontal line represents the limit of 10% reduction in the FEV_1 as compared to the baseline value. Intermittent vertical lines represent the limits of achieved ventilation rates as multiples of the baseline FEV_1. (FEV_1 = forced expiratory volume in the first second).

Table 1. Characterization of the overall sample and according to FEV_1 responses after eucapnic voluntary hyperventilation (EVH).

Variables	ALL (n=72)	POSITIVE EVH RESPONSE (n=36)	NEGATIVE EVH RESPONSE (n=36)	p
Sex				
Male (%)	33 (45.8)	17 (47.2)	16 (44.4)	0.813*
Female (%)	39 (54.2)	19 (52.8)	20 (55.6)	
Age (Years $\pm$ SD)	14.52±3.45	13.14±2.59	12.89±2.88	0.697**
Height (cm $\pm$ SD)	154.8±10.52	155.0±11.14	154.6±10.33	0.885**
Weight (kg $\pm$ SD)	50.16±12.89	52.27±14.02	48.13±11.65	0.287**
FEV_1				
Baseline ($L.sec^{-1}$) (Median and IQR)	2.29 (1.87-2.80)	2.19 (1.90-2.64)	2.46 (1.84-2.91)	0.295ŧ
% predicted (Median and IQR)	86.50 (76.23-96.75)	81.80 (73.63-95.50)	91.55 (91.55-101.60)	0.108 ŧ
Maximum fall as % of basal (Median and IQR)	10.13 (22.50 - 4.60)	22.34 (16.75-39.23)	4.66 (2.47- 6.83)	<0.001 ŧ
ACT score n (%)				
≤ 19	23 (32%)	15 (42%)	8 (22%)	0.077*
> 19	49 (68%)	21 (58%)	28 (78%)	

Values are expressed as frequency (%), mean ± standard deviation and median (IQR). POSITIVE RESPONSE = individuals with a fall in $FEV_1 \geq 10\%$ after eucapnic voluntary hyperventilation (EVH) compared to baseline. NEGATIVE RESPONSE = individuals with a FEV_1 fall <10% after EVH compared to baseline. FEV_1 = forced expiratory volume in the first second. IQR = interquartile range. ACT = Asthma control test. * Chi-squared test, **t-test, ŧ Mann Whitney test.

Table 2. Association between bronchial responses and ventilation rates achieved at the first EVH challenge (A) and at the second challenge in those with a negative response to the first challenge (B).

A- Ventilation rates and bronchial response to the first EVH challenge (n = 72)

Ventilation rate	EIB-cr* Positive (n=36)	EIB-cr* Negative (n=36)
Low ($<17x\ FEV_1$)	09 (50.0%)	09 (50.0%)
Intermediate ($\geq 17x\ FEV_1 - \leq 21x\ FEV_1$)	15 (51.7%)	14 (48.3%)
High ($>21x\ FEV_1$)	12 (48.0%)	13 (52.0%)

Chi-squared test for trend p-value = 0.878

B- Ventilation rates and bronchial response at the second EVH challenge of individuals with a negative test on the first day. (n = 36)

Ventilation rate	EIB-cr* Positive (n= 14)	EIB-cr* Negative (n=22)
Low ($<17x\ FEV_1$)	02 (14.4%)	06 (27.3%)
Intermediate ($\geq 17x\ FEV_1 - \leq 21x\ FEV_1$)	06 (42.8%)	09 (40.9%)
High ($>21x\ FEV_1$)	06 (42.8%)	07 (31.8%)

Chi-squared test for trend p-value = 0.349

*EIB-cr = Exercise-induced bronchospasm compatible response

Figure 1

Click here to access/download;Figure;Figure 1.jpg

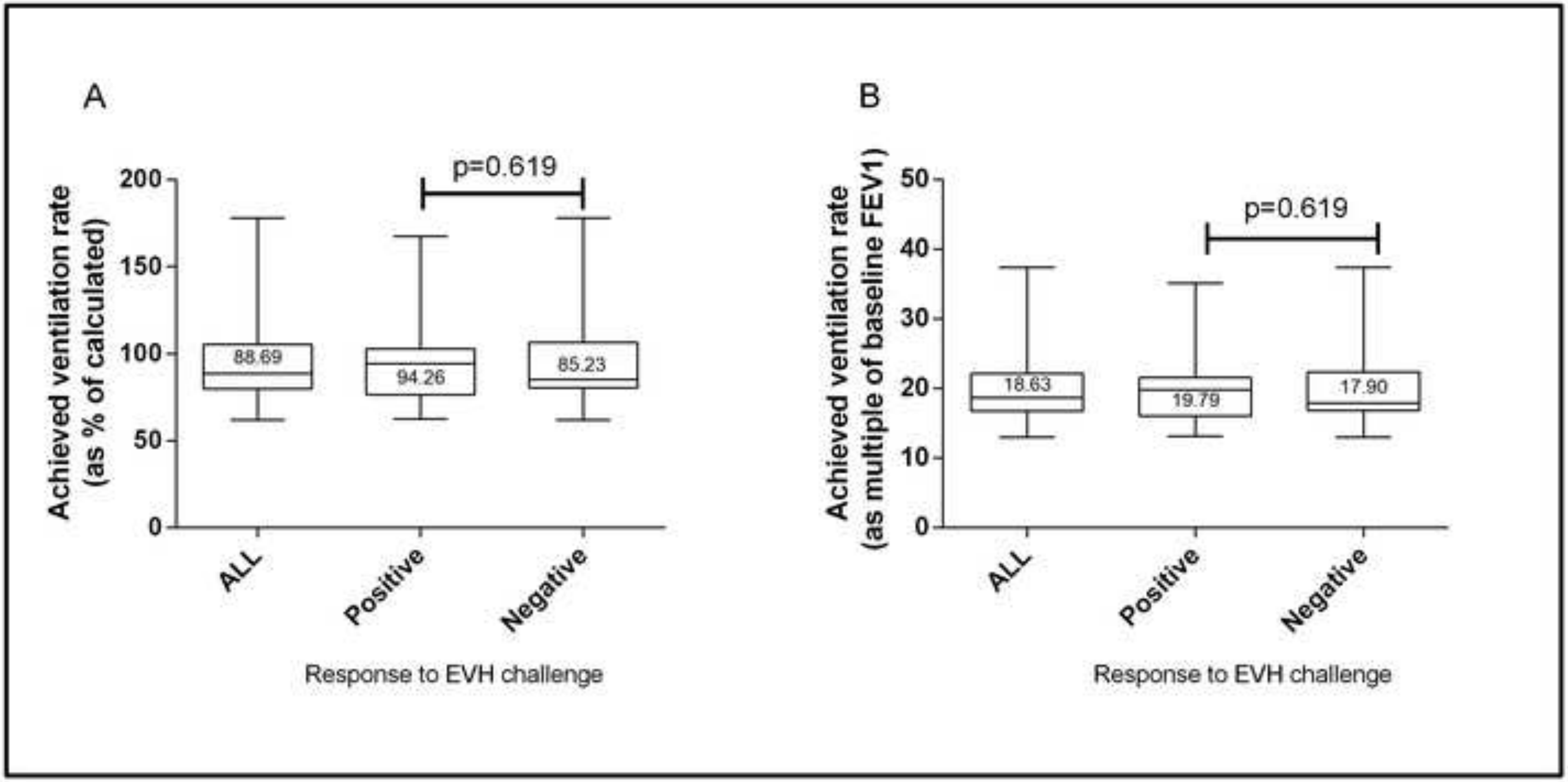
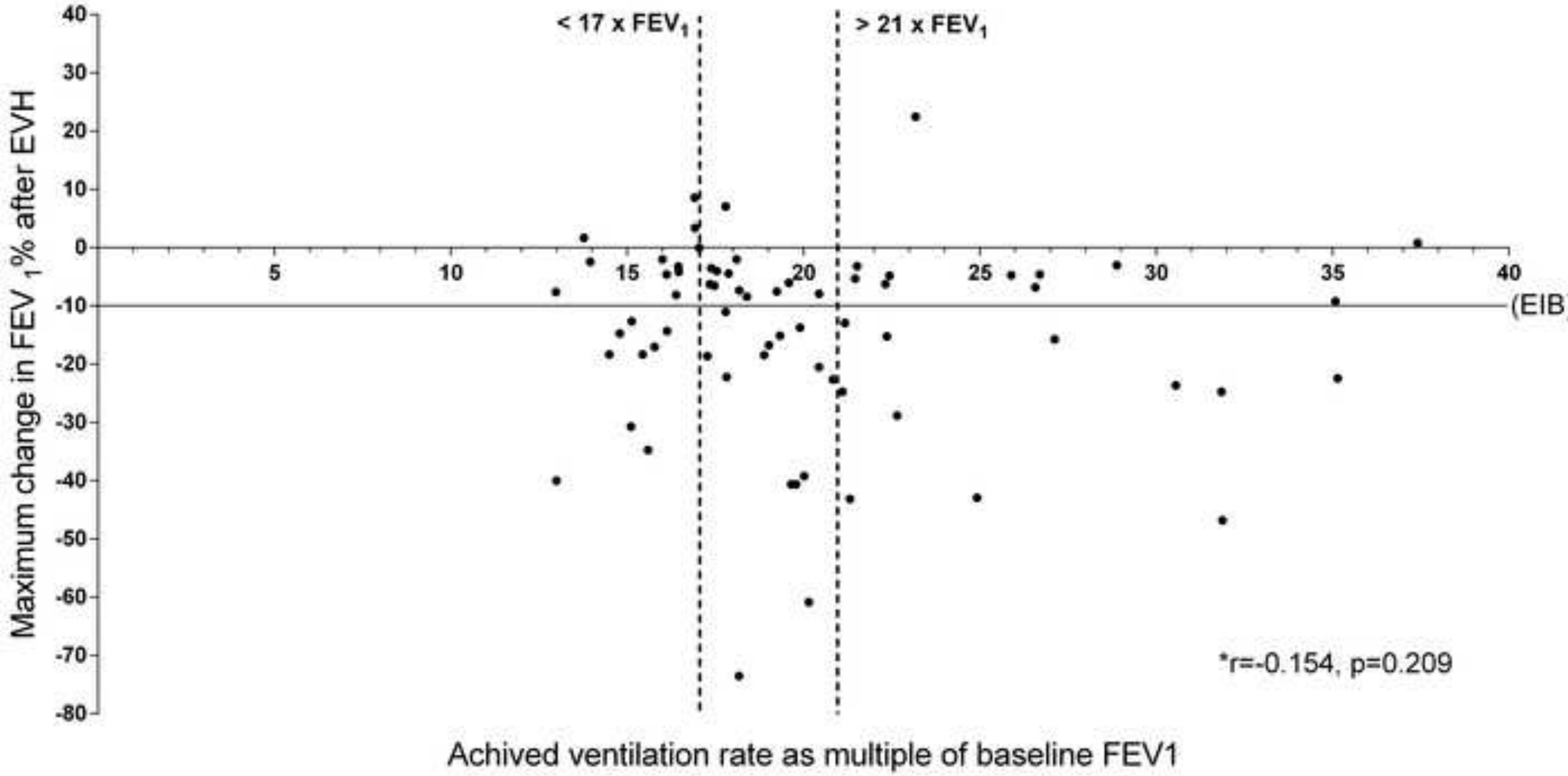


Figure 2



< 17 x FEV1
> 21 x FEV1
Maximum change in FEV 1 % after EVH
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
5
10
15
20
25
30
35
40
(EIB)
*r=-0.154, p=0.209
Achived ventilation rate as multiple of baseline FEV1