Physiology and Pharmacology 29 (2025) 123-134
Clinical Research Article

Evaluation of bronchial response among occupationally exposed vulcanizers in calabar municipality, cross river state -nigeria

Utionkpan L Paul[1*], Helyn A Ikem[1], Cecilia Peter[1], Solomon Beshel[2]

1. Human Physiology, University of Calabar, Calabar, Nigeria
2. Zoology and Environmental Biology, University of Calabar, Calabar, Nigeria

ABSTRACT

Introduction: Histamine directly interacts with airways smooth muscles to initiate contraction. This occurs even at low concentrations among individuals predisposed to increased airway inflammation and asthma.

Methods: A digital vitalograph, nebulizer, histamine, and pulse oximeter were used in this research. A total of one hundred and sixty subjects were selected and categorized into two groups; Group 1 (Test subject) and Group 2 (Control), each group contained eighty (80) subjects. Group 1 comprised occupationally exposed vulcanizers and Group 2 comprised selected students from the University of Calabar as control. Both groups comprised young male subjects of equal age (20-40 years), devoid of pre-existing respiratory disorders or on any medication(s). Demographic parameters were used to obtain sufficient information for overall analysis. Lung parameters (FVC, FEV1, PEFR, and FEV1%) were evaluated using a Vitalograph Spirometer.

Results: Basal measurement showed that Group 1 had a moderate decrease in lung volumes (FVC, FEV1, PEFR, and FEV1%) of 65 subjects (representing 81.25%) and a mild decrease in 15 subjects (18.75%); all the subjects in Group 2 showed a mild decrease in lung volumes. Inhalation of histamine mist of different concentrations showed that Group 1 had a severe decrease in lung volumes of 70 subjects (87.5%) and a mild decrease in 10 subjects (12.5%). All Subjects in Group 2 showed a mild decrease in lung volumes.

Conclusion: Histamine provocative test helps to evaluate asthma signs and symptoms. Airways Hyper reactiv-ity is associated with inflammation as a consequence of airway hyperreflexia. It is evidenced that associated pollutants and their chronic inhalation by the vulcanizers have a retrogressive impact on their airways which manifests with hyper response an indication for asthma signs.

Keywords:
Spirometry
Vulcanizers
Histamine
Bronchial responses

* Corresponding author: Utionkpan Linna Paul, utionkpanlinna@unical.edu.ng
Received 28 October 2023; Revised from 29 September 2024; Accepted 5 October 2024

Citation: Utionkpan Paul L, Ikem HA, Peter CA, Beshel SB. Evaluation of bronchial response among occupationally exposed vulcanizers in calabar municipality, cross river state -nigeria. Physiology and Pharmacology 2025; 29: 123-134. http://dx.doi.org/10.61186/phypha.29.2.123

Introduction

Chronic exposure and inhalation of sulphuric fumes, and black soot (black carbon) with associated pollutants, is known to cause increased inflammation and structural remodeling in the respiratory system (Niranjan and Thakur 2017). Damaged tyres (vehicles and other automobiles) caused by mechanical wear and tear are patched by vulcanizers. The chemical process that involves heating tires with sulphur in an accelerator and activator at 140–160°C is known as vulcanization. About 25 to 75 percent of tyres prematurely failed due to mechanical damage, comprising expansion and punctures (Akiba and Hashim 1997). Exposure to carbon fumes, particulate matter, inhalable dust concentration, and other hazardous substances like sulphuric fumes and carbon monoxides from the burning chambers increases the risk of respiratory inflammation and the shear stress generates a cascade of mediators that triggers sensory neuronal which are transmitted to the afferent parasympathetic autonomic nervous system leading to constriction of airway smooth muscles (Anderson and Brannan 2003; Córdova-Guerrero et al., 2013; Marone et al., 2001). Bronchi are the conduit for the movement of air in and out of the lungsContraction of airway smooth muscle causes the bronchi to narrow, restricting airflow into the lungs.(Borges et al., 2008; Borges et al., 2011; Ferraz et al., 2006; Martin et al., 2000). Pulmonary function tests utilize basic lung parameters such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), and FEV_1/FVC ratio (FEV_1%) to evaluate lung function as well as predict vulnerable individuals to respiratory diseases such as asthma, etc (Araujo and Holanda 2010; Beydon et al., 2007; Fitch et al., 2008; Pauwels et al., 2001). Some research evaluated the role of carbon-containing particulate matter component, particularly black carbon, and opined that it has a systemic role in aggravating inflammation of the respiratory system and other deleterious health challenges (Brudno et al., 1994; Gotshall 2002; Jensen et al., 2001). Chronic inhalation of sulphuric fumes is associated with irritation of the respiratory tract and eyes (lacrimation), bronchitis, cough, and chest tightness, often responsible for retrogressive changes in lung function (Holzer et al., 2002; Knapp et al., 1991; McFadden Jr and Gilbert 1994).

Many studies explained the role of persistent exposure to hydrocarbon pollutants that elicits inflammation of airways by activating histamine production (Brannan et al., 2003; Caldeira et al., 2006; Marone et al., 2001). Histamine is a potent inflammatory mediator, commonly associated with allergic reactions, promoting vascular and tissue changes with high chemo-attractant activities (Cockcroft 2003; Cockcroft and Davis 2006). Bronchi are usually affected by exposure to hazardous substances (Joos 2003; Joos et al., 2003; Martin et al., 2000). In Nigeria, the presence of poorly maintained roads has necessitated an increased number of vulcanizers on commercial and non-commercial streets of major cities because of its low capital start-up and high profits.

This research investigated bronchi response in vulcanizers' airways to chronic inhalation of black soot and associated pollutants with the aim to assess their vulnerability to asthma, a leading respiratory disease in Nigerian hospitals.

Materials and Methods

Materials used in the study include a hand-held nebulizer, Vitalograph Alpha Touch Spirometer (Model 6000), weighing balance, long ruler, stopwatch, histamine, and distilled water.

Study Subjects

One hundred and sixty subjects were recruited for this study and comprised of eighty subjects each for Test and Control groups. Test subjects were vulcanizers actively involved in patching tyres by the roadside in Calabar Metropolis, Cross River State. Inclusion criteria involved a male subject aged between 20-40 years working as a vulcanizer for not less than two years, free from any pre-existing illness was selected as Test subjects. Male students from the University of Calabar of similar age, body weight, and height, with supposedly zero exposure to hazardous gases and free from any illness, were used as Control subjects. Ethical consent with registration number: CRS/MH/HREC/2021/710 was obtained from Cross River State Ministry of health, Calabar.

Exclusion Criteria

Subjects above the age limit or on any medication were excluded from the study.

Method

Experimental Design

TABLE 1: Showing mean values of Demographic Parameters

GROUPS	AGE (Yrs)	OXYGEN SATURATION (%)	CHEST CIRCUMFERENCE (cm)	HEIGHT (cm)	WEIGHT (kg)	BMI
CONTROL	23.85±0.37	95.63 ±0.17	86.64 ±0.26	169±0.27	57.85 ± 0.38	20.02 ±0.14
TEST	24.68±0.37	95.85±0.17	86.70±0.26	169±0.27	58.60±0.38	20.38± 0.14

Structured questionnaires were administered, to determine the inclusion of subjects in the study. The number of subjects recruited for the study was determined by the sample size formula as described by Slovin (Slovin 1960). Histamine dose was graded into Low dose and High dose and subjects were exposed to the two-dose concentrations to assess bronchial response using their lung function parameters. This was determined using a vitalograph Spirometer. Height, and weight were measured with a ruler and weighing balance.

Dose Formulation

Histamine powder was used in the formulation according to the method postulated by Cockcroft (Cockcroft et al., 1983). The strength of the stimulus is its concentration of solutes delivered to the lower airways.

Low Dose (4mg)

Low dose concentration was formulated by dissolving 0.04g w/v of Histamine in 100ml distilled water.

High Dose (16mg)

High dose concentration was formulated using the same method to dissolve 0.16g w/v of Histamine in 100ml distilled water.

Evaluation of Bronchial Response and Lung Function

Vitalograph-Spirometer (Alpha touch 6000, Uk) was used to evaluate bronchial response. The subjects were instructed on the protocols before the maneuver (measurements) to achieve the best spirometric result. Three to five maneuvers were performed according to the subject's adherence to the protocols and this was repeated at least three times with acceptable efforts. Histamine dose was administered starting with a low dose. Acceptable spirometric values for FVC, FEV_1, PEFR, and FEV_1% after administration were used to assess bronchial response.

The spirometric values were compared with the predicted values according to the reference recommended by the American Thoracic Society (ATS) criteria, 2005.

Procedure

The Subjects were instructed on the evaluation protocols. Three maneuvers were measured (Basal, Low dose, and High dose). Basal values were recorded before administration of the histamine dose. Histamine mists (4mg/ml and 16mg/ml) were introduced using a hand-held Nebulizer for 2 minutes beginning with a low dose (4mg/ml). The subjects freely inhaled the histamine mists for 2 minutes and allowed for 1 minute before the bronchial response was assessed using a Vitalograph Spirometer. The same protocols were used in the high dose (16mg/ml). The Nebulizer was rinsed with distilled water after each dose administration. The bronchial response was determined by comparing basal and dose-administered values with predicted values.

Statistical Analysis

The results were presented as Mean ± standard deviation (SD). The data were analyzed using SPSS software and compared using Students' T-test. The probability level of $P < 0.001$ was considered statistically significant.

Result

Comparison of demographic parameters between Vulcanizers and Control subjects

In this study, the results were compared between vulcanizers (test group) and control subjects and presented as mean ± SD. The results of the demographic parameters of vulcanizers were presented as; Age (24.68±0.37), Oxygen saturation (95.85±0.17), Weight (51.63±0.38), Chest circumference (86.70±0.26), Height (169.74±0.30) and Body mass index (20.38±0.15) and control subjects were presented as; Age (23.85±0.30), Oxygen satura-

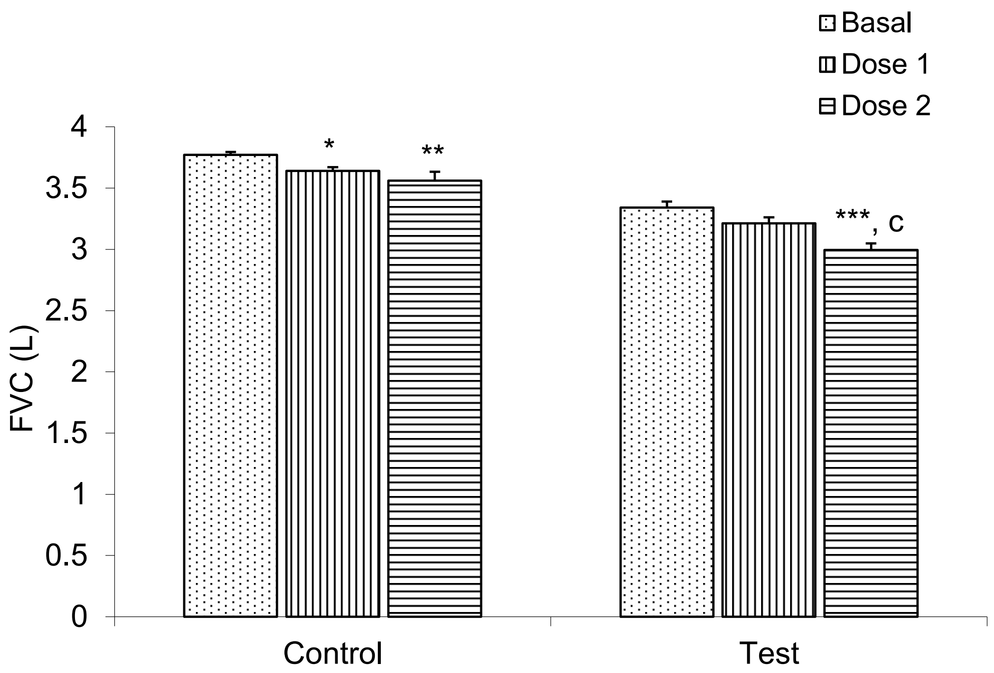

FIGURE 1. Shows Basal, first dose and second dose in forced vital capacity between control and test group. Values are expressed as mean ±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

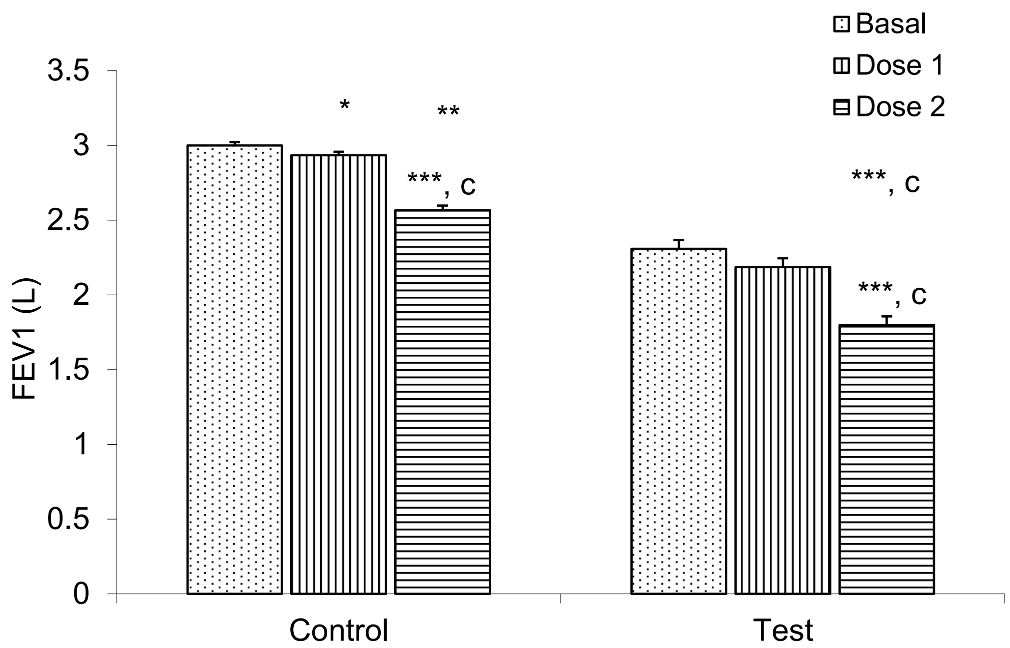

FIGURE 2. Shows Basal, first and second dose in Forced expirartory volume in one second between control and test group. Values are expressed as mean ±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

tion (95.63±0.21), Weight (50.62±0.42), Chest circumference (86.64±0.25), Height(169.75±0.13) and Body mass index (20.02±0.14).There was no significant difference between the test and control subjects.

Figure 1-6 shows a comparison of demographic parameters (Age, Oxygen saturation, weight, Chest circumference, Height, and Body mass index) between vulcanizers and control subjects.

Bronchial Response between Vulcanizers and Control Subjects

Results were compared between vulcanizers and Con-

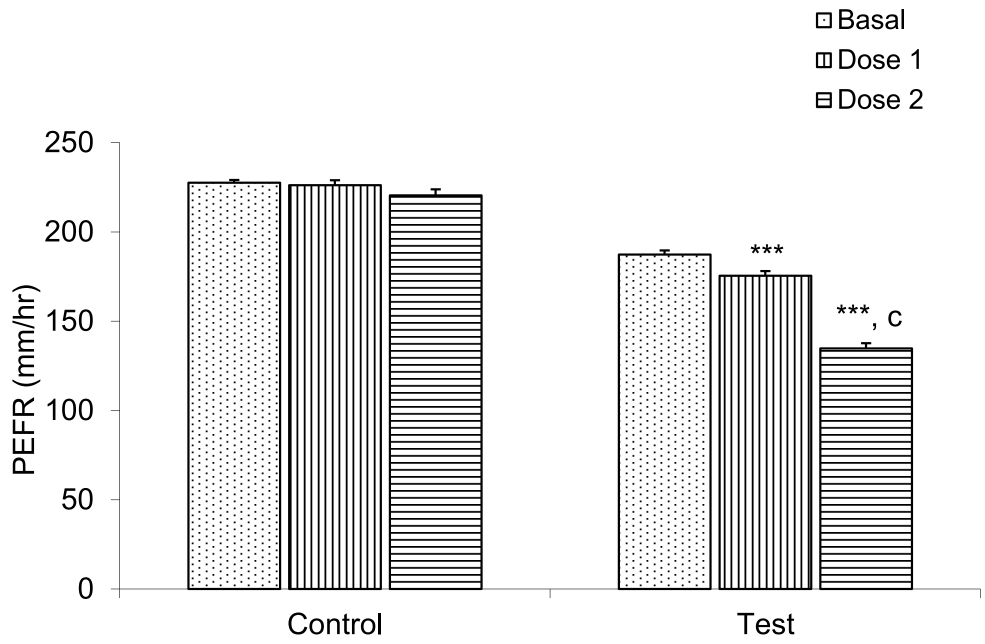

FIGURE 3. Shows Basal, first and second dose in peak expiratory flow rate between control and test group. Values are expressed as mean ±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

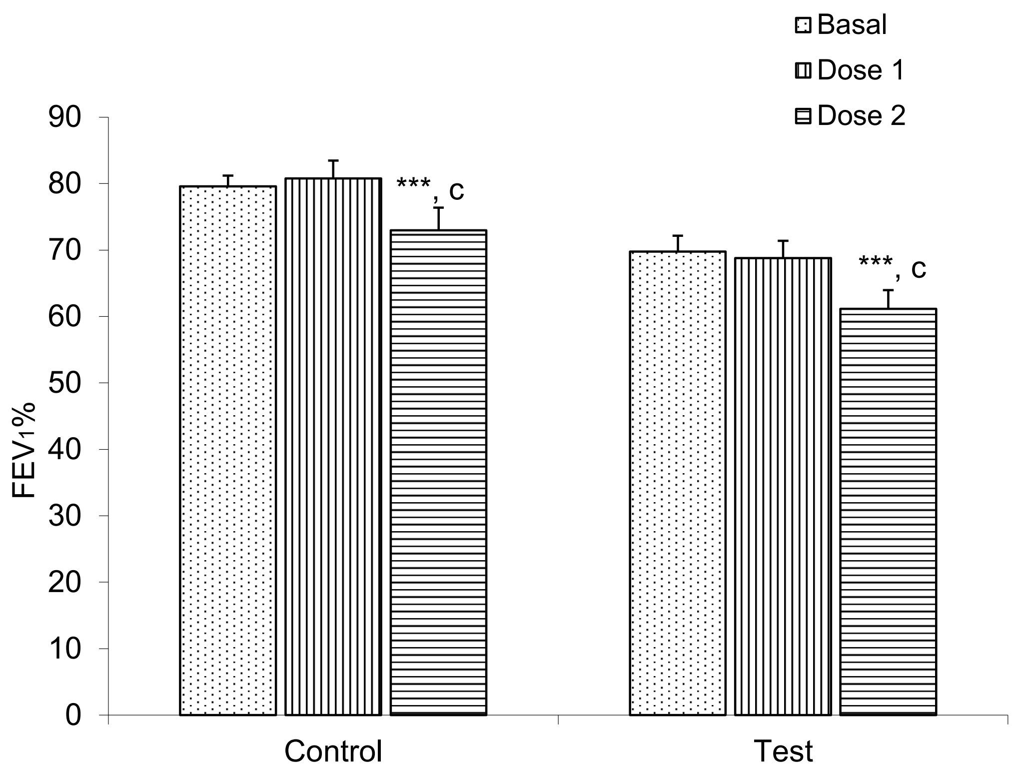

FIGURE 4. Shows Basal, Low and High dose in FEV1% between Control subjects and Vulcanizers. Values are expressed as mean ±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

trol subjects. Result of spirometric values among vulcanizers were presented as, FVC (Basal 3.34±0.05); (Low Dose 3.21±0.05); (High Dose 2.99±0.05), FEV_1 (Basal 2.30±0.05); (Low Dose 2.18±0.05); (High Dose 1.79±0.05), PEFR (Basal 187.34±2.36); (Low Dose 175.41±2.59); (High Dose 134.82±2.81), FEV1% (Bas-

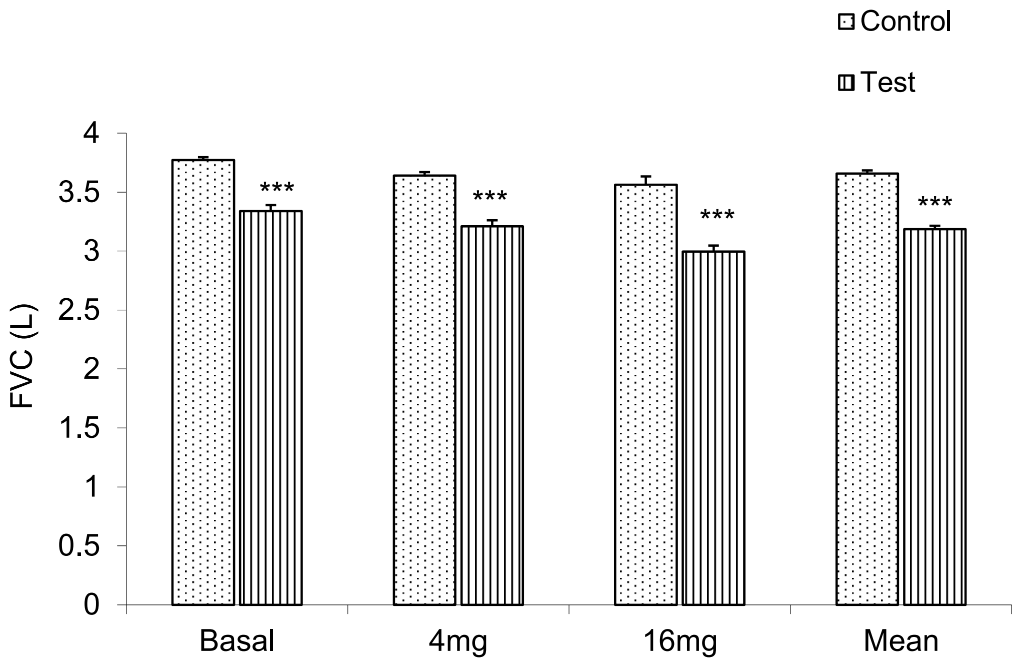

FIGURE 5. Shows mean response in Forced vital capacity between control Subjects and Vulcanizers. Values are expressed as mean ±SD *** = p<0.001 vs control.

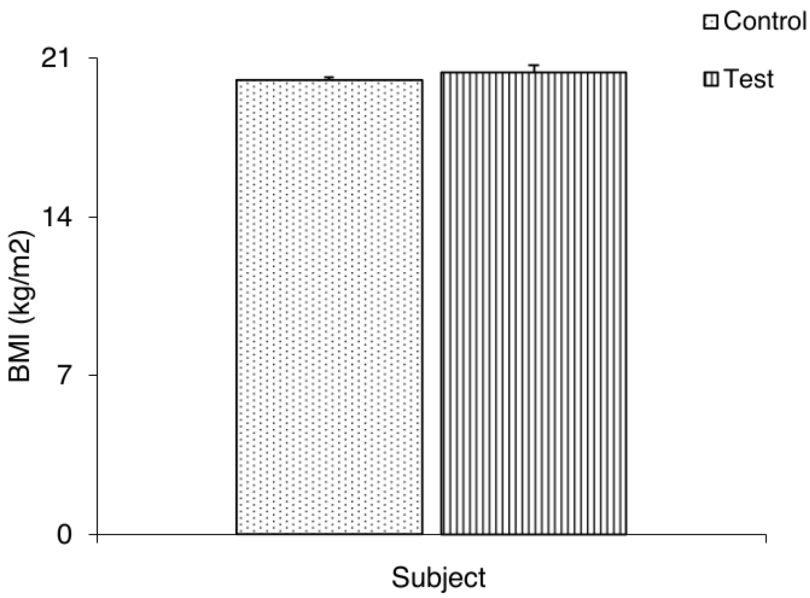

FIGURE 6. Shows mean value of body mass index between Control subjects and Vulcanizers. Values are expressed as mean ±SD.No significant difference between the groups.

al 69.79± 1. 72); (Low Dose 68.78±1.84); (High Dose 61.16±2.11) compared with results of spirometric values in Control subjects presented as, FVC (Basal 3.77±0.02); (Low Dose 3.64±0.02); (High Dose 3.56±0.07); FEV_1 (Basal 2.99±0.02); (Low Dose 2.93±0.02); (High Dose 2.56±0.02), PEFR (Basal 227.53±1.61); (Low Dose 226.18±2.71); (High Dose 220.49±3.41), FEV1% (Basal 79.57±0.40); (Low Dose 80.96±0.62); (High Dose 72.96±0.98).

Spirometric parameters (FVC, FEV_1, PEFR, and FEV1%) among vulcanizers were found to be significantly lower (P<0.001) compared to the Control subjects. At high doses, vulcanisers experience a greater decrease in thespirometric values as a result of bron-

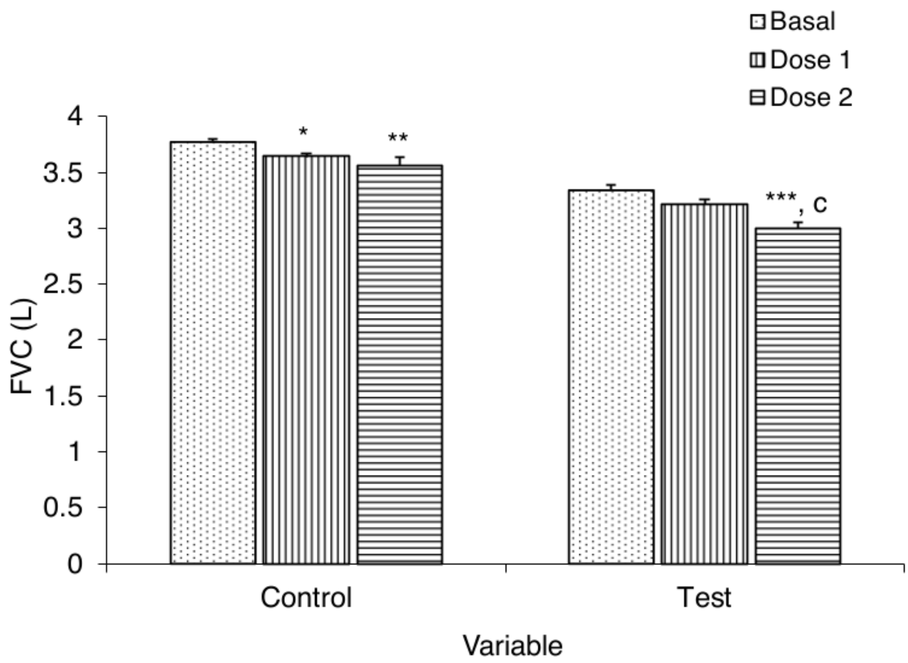

FIGURE 7. Shows Basal, first dose and second dose in forced vital capacity between control and test group. Values are expressed as mean±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

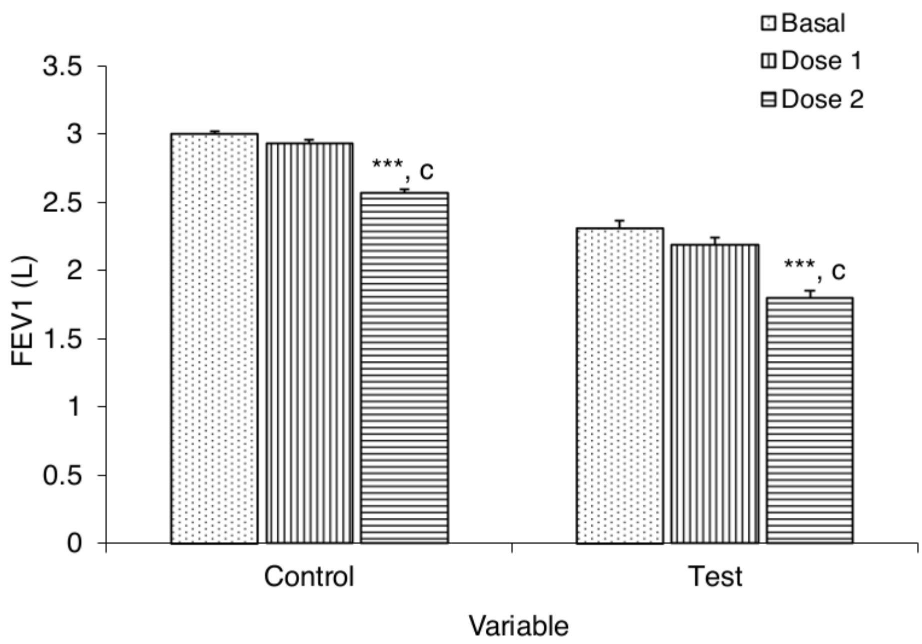

FIGURE 8. Shows Basal, first and second dose in Forced expirartory volume in one second between control and test group. Values are expressed as mean ±SD. *** = p<0.001 vs basal. c = p<0.001 vs dose 1.

cho-constriction.

Figure 7–10 shows a comparison of FVC, FEV1, PEFR, and FEV_1% between vulcanizers and Control subjects at different histamine doses. Figure 11 shows the mean values of FVC to dose-response between vulcanizers and control subjects.

Discussion

Histamine is a naturally occurring biological substance in body that plays vital role in various functions including immune response. Primarily known for its involvement in allergic reactions, where its release by mast cells leads to symptoms like running nose, sneez-

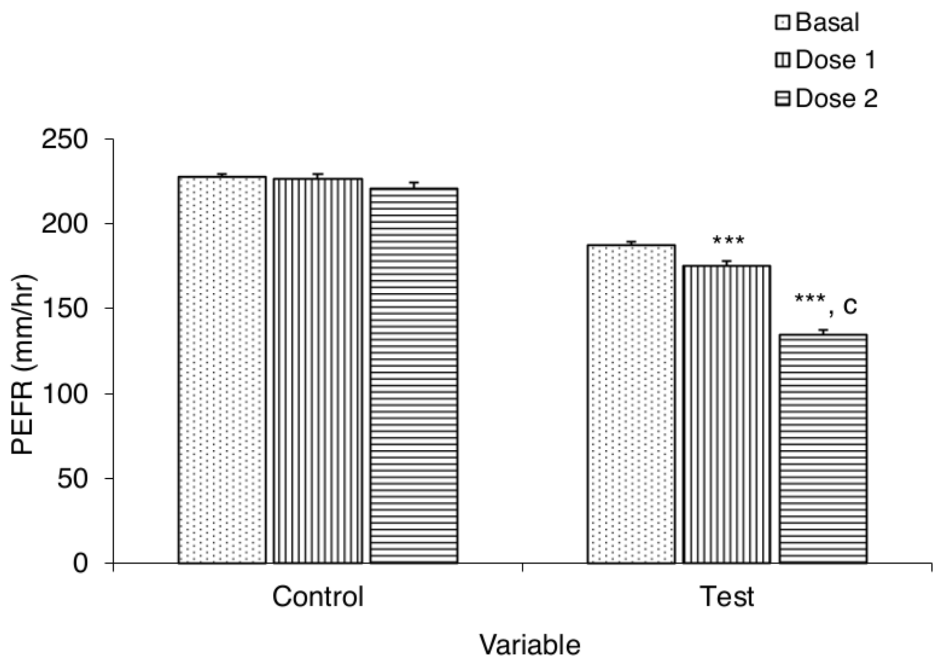

FIGURE 9. Shows Basal, first and second dose in peak expiratory flow rate between control and test group. Values are expressed as mean ±SD. *** = $p<0.001$ vs basal. c = $p<0.001$ vs dose 1.

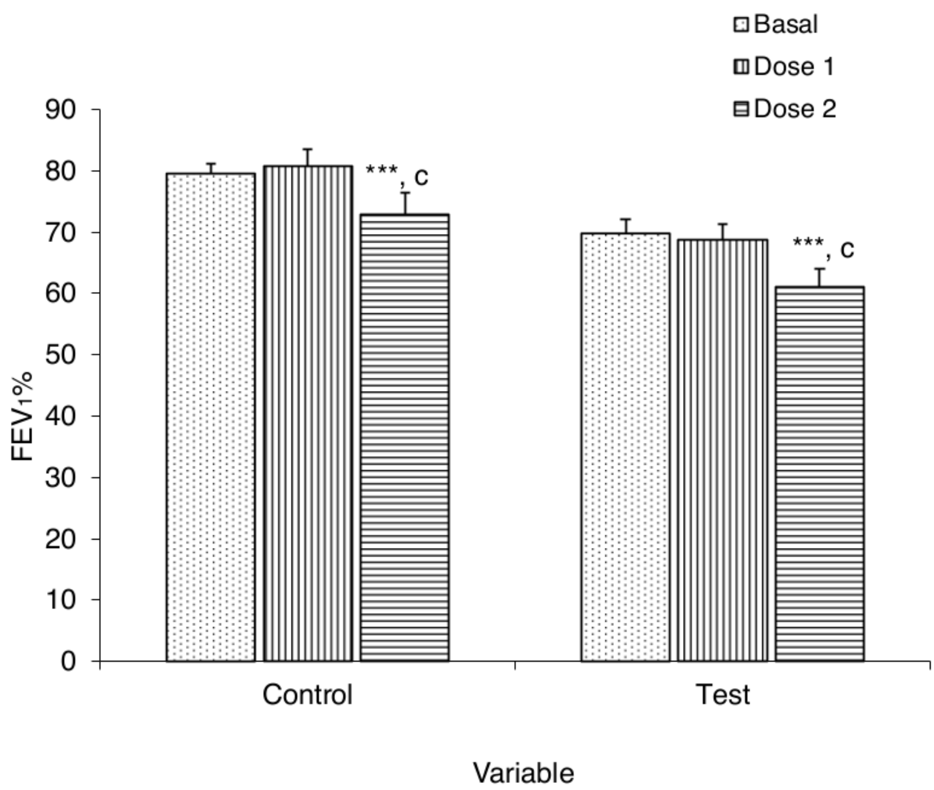

FIGURE 10. Shows Basal, Low and High dose in FEV1% between Control subjects and Vulcanizers. Values are expressed as mean ±SD. *** = $p<0.001$ vs basal. c = $p<0.001$ vs dose 1.

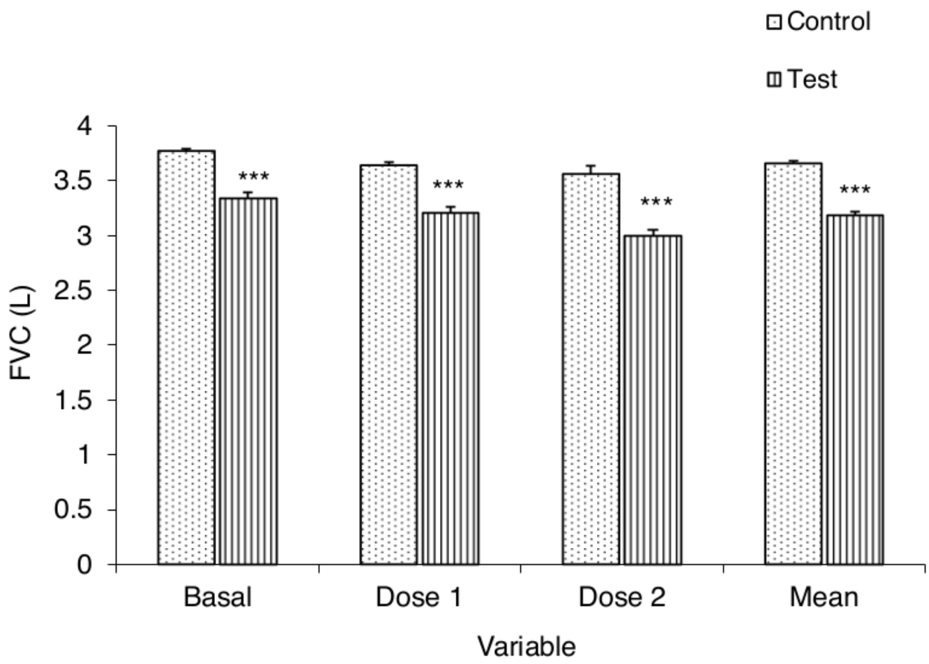

FIGURE 11. Shows mean response in Forced vital capacity between control Subjects and Vulcanizers. Values are expressed as mean ±SD *** = p<0.001 vs control.

ing, etc. It plays a role by constricting bronchial smooth muscles, leading to narrowing of the airways even at low dose, as seen in atopic individuals with heighten sensitivity than normal subjects(Van Schoor et al.,2000; Vianna et al.,2002). It was reported that histamine induces contraction of human bronchi as one of its biological effects(Curry 1946; TsangKW 2004). According to American Lung Association, long-term exposure to black carbon and associated pollutants can cause chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema (Pogson et al., 2008; Ro 2000; Sterk et al., 1993). Smoking is one of the main risk factors for developing COPD, non smokers may also develop COPD (Parsons and Mastronarde 2005; Rundell and Jenkinson 2002; Rundell et al., 2000). Spirometry is the most common and sensitive pulmonary function test, widely used for many years in various studies. It is often employed to assess lung function and predict asthma(Boulet et al., 1997; De Meer et al., 2004; Rodrigues et al., 2010). Histamine directly activates H1 receptors in airway smooth muscles, leading to bronchoconstriction (Bimestral 2012; Randolph 2009; VAN DER LENDE 1993). Bronchi provocative test was employed to investigate the effects of chronic inhalation of sulphur fumes used by vulcanizers and other associated pollutants like black soot on their respiratory system and predict vulnerability to asthma disease. Histamine is chosen as a provocator in bronchial challenge tests because it plays a key role in inflammatory cellular responses and helps reveal airway sensitivity (Marone et al., 2001). The results in this study indicated that demographic parameters showed no significant difference (P>0.001) between test and Control subjects. When subjects were exposed to a low dose of histamine, there was no significant change in the spirometric values of control subjects; however, exposure to a high dose resulted in a pronounced decrease.This was also reported by Lotvall et al (1998), that healthy individuals required high doses (8-100mg/ml) of a provocator (methacholine or histamine) to cause airway resistance. Spirometric values were reduced among vulcanizers suggesting inflammation and reduced lung function. A study by Rafferty *et al* (1987) has also opined that inflammation is responsible for the release of histamine that exerts tension on the walls of airway smooth muscles with an abnormal decrease in spirometric values of FEV_1, FVC, PEFR, as well as FEV1% % (Rafferty et al., 1987). A report by Echazarreta *et al* (2001) also confirmed that histamine provoked bronchial response when assessed the values in FVC, FEV_1, PEFR, and FEV_1% (Echazarreta et al., 2001). Black Soots from burning chambers and Sulphuric fumes frequently inhaled by vulcanizers can cause damage to the walls of the respiratory tree which makes the walls susceptible to inflammation and histamine secretion (Rodwell et al., 1992). From the result of this study, bronchi response occurred in Vulcanizers when a low dose (4mg) of histamine concentration was inhaled. There was hyperreactivity when a high dose(16mg) of histamine concentration was inhaled and a significant reduction was revealed in spirometric values (FVC, FEV_1, PEFR, and FEV_1%). Hyper bronchi response is indicative of inflammation of the airways, and this correlates with responses of most vulcanizers to have been in the occupation for more than five years. The FEV1% % was significantly lower in vulcanizers, this correlates with evidence from the work of Gauderman *et al.,* (Gauderman et al., 2007)on long-term daily exposure to gas pollutants which affected lung parameters (FEV_1 and FVC) in healthy adults even at low concentrations. Reduction in FEV_1% below 70% alongside with FVC, FEV_1, and PEFR is suggestive of vulnerability to having asthma disease in future if not properly monitored to reduce rate of exposure and inhalation. Decreased in FVC, FEV1, PEFR and FEV_1%, illustrates that continuous exposure will keep vulcanizers at high risk of chronic obstructive pulmonary disease. This corresponds with the work of Rahimi *et al* (2019) that concluded individuals exposed to petroleum fumes and associated products have decreased spirometric values. Research by Svedahl *et al* (2009) also documented a significant decrease in lung function parameters in individuals due to fumes from cooking gas (Svedahl et al., 2009). Pollutants like fumes, soot, smokes, particulate matters and fumes from chemicals have irritation on the airway mucosa (Jensen et al., 2001) and has negative impact on pulmonary function.

Conclusion

This study demonstrated that vulcanizers exhibit significant airway hyperresponsiveness, characterized by bronchoconstriction, following histamine administration. Chronic inhalation of sulfuric fumes, black soot, and other pollutants from automobile exhausts is known to worsen airway inflammation in vulcanizers, increasing their risk of developing obstructive pulmonary diseases. Therefore, it is essential to use protective gear such as nose masks and work in safer, well-ventilated chambers to minimize exposure and safeguard respiratory health.

Limitation of the Study

This is an experimental research article. No grant was given from the institution or government. The experimental setting required lots of time and energy to convince subjects to participate in the study.

Acknowledgements

This study has no funding

Conflict of interest

The authors declared no conflicts of interest.

Ethics approval

Ethical consent was obtained from Ministry of Health, Calabar, Health Research Ethics Committee (HREC) Calabar, Cross River State with registration number: CRS/MH/HREC/2021/710.

References

Akiba M, Hashim A S. Vulcanization and crosslinking in elastomers. Progress in Polymer Science 1997; 22: 475-521. https://doi.org/10.1016/S0079-6700(96)00015-9

Anderson S D, Brannan J D. Methods for “indirect” challenge tests including exercise, eucapnic voluntary hyperpnea, and hypertonic aerosols. Clinical Reviews in Allergy & Immunology 2003; 24: 27-54. https://doi.org/10.1385/CRIAI:24:1:27

Araujo Z T d S, Holanda G. Does the BODE index correlate with quality of life in patients with COPD? Jornal Brasileiro de Pneumologia 2010; 36: 447-452. https://doi.org/10.1590/S1806-37132010000400009

Beydon N, Davis S D, Lombardi E, Allen J L, Arets H G, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. American Journal of Respiratory and Critical Care Medicine 2007; 175: 1304-1345. https://doi.org/10.1164/rccm.200605-642ST

Bimestral P. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma-2012. Jornal Brasileiro de Pneumologia 2012; 38.

Borges M, Ferraz E, Terra-Filho J, Vianna E. Protective effect of bronchial challenge with hypertonic saline on nocturnal asthma. Brazilian Journal of Medical and Biological Research 2008; 41: 209-214. https://doi.org/10.1590/S0100-

879X2008000300006

Borges M d C, Ferraz E, Vianna E O. Bronchial provocation tests in clinical practice. Sao Paulo Medical Journal 2011; 129: 243-249. https://doi.org/10.1590/S1516-31802011000400008

Boulet L-P, Laviolette M, Turcotte H, Cartier A, Dugas M, Malo J-L, et al. Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. Chest 1997; 112: 45-52. https://doi.org/10.1378/chest.112.1.45

Brannan J, Gulliksson M, Anderson S, Chew N, Kumlin M. Evidence of mast cell activation and leukotriene release after mannitol inhalation. European Respiratory Journal 2003; 22: 491-496. https://doi.org/10.1183/09031936.03.00113403

Brudno D S, Wagner J M, Rupp N T. Length of postexercise assessment in the determination of exercise-induced bronchospasm. Annals of Allergy 1994; 73: 227-231.

Caldeira R D, Bettiol H, Barbieri M A, Terra-Filho J, Garcia C A, Vianna E O. Prevalence and risk factors for work related asthma in young adults. Occupational and Environmental Medicine 2006; 63: 694-699. https://doi.org/10.1136/oem.2005.025916

Cockcroft D W. Bronchoprovocation methods: direct challenges. Clinical reviews in allergy & immunology 2003; 24: 19-26. https://doi.org/10.1385/CRIAI:24:1:19

Cockcroft D W, Berscheid B A, Murdock K Y. Unimodal distribution of bronchial responsiveness to inhaled histamine in a random human population. Chest 1983; 83: 751-4. https://doi.org/10.1378/chest.83.5.751

Cockcroft D W, Davis B E. Mechanisms of airway hyperresponsiveness. Journal of allergy and clinical immunology 2006; 118: 551-559. https://doi.org/10.1016/j.jaci.2006.07.012

Córdova-Guerrero I, San Andrés L, Leal-Orozco A E, Padrón J M, Cornejo-Bravo J, León F. New strategy toward the diverted synthesis of oxidized abietane diterpenes via oxidation of 6, 7-dehydroferruginol methyl ether with dimethyldioxirane. Tetrahedron Letters 2013; 54: 4479-4482. https://doi.org/10.1016/j.tetlet.2013.06.048

Curry J J. The effect of antihistamine substances and other drugs on histamine bronchoconstriction in asthmatic subjects. The Journal of Clinical Investigation 1946; 25: 792-799. https://doi.org/10.1172/JCI101765

De Meer G, Marks G, Postma D. Review direct or indirect stimuli for bronchial challenge testing: what is the relevance for asthma epidemiology? Clinical & Experimental Allergy 2004; 34. https://doi.org/10.1111/j.1365-2222.2004.01830.x

Echazarreta A, Gomez F, Ribas J, Sala E, Barbera J, Roca J, et al. Pulmonary gas exchange responses to histamine and methacholine challenges in mild asthma. European Respiratory Journal 2001; 17: 609-614. https://doi.org/10.1183/09031936.01.17406090

Ferraz E, Borges M C, Terra-Filho J, Martinez J A, Vianna E O. Comparison of 4 AM and 4 PM bronchial responsiveness to hypertonic saline in asthma. Lung 2006; 184: 341-346. https://doi.org/10.1007/s00408-006-0017-0

Fitch K D, Sue-Chu M, Anderson S D, Boulet L-P, Hancox R J, McKenzie D C, et al. Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008. Journal of Allergy and Clinical Immunology 2008; 122: 254-260. e7. https://doi.org/10.1016/j.jaci.2008.07.003

Gauderman W J, Vora H, McConnell R, Berhane K, Gilliland F, Thomas D, et al. Effect of exposure to traffic on lung development from 10 to 18 years of age: a cohort study. The Lancet 2007; 369: 571-577. https://doi.org/10.1016/S0140-6736(07)60037-3

Gotshall R W. Exercise-induced bronchoconstriction. Drugs 2002; 62: 1725-1739. https://doi.org/10.2165/00003495-200262120-00003

Holzer K, Anderson S D, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. Journal of allergy and clinical immunology 2002; 110: 374-380. https://doi.org/10.1067/mai.2002.127784

Jensen L K, Larsen A, Mølhave L, Hansen M K, Knudsen B. Health evaluation of volatile organic compound (VOC) emissions from wood and wood-based materials. Archives of Environmental Health: An International Journal 2001; 56: 419-432. https://doi.org/10.1080/00039890109604477

Joos G F. Bronchial hyperresponsiveness: too complex to be useful? Current Opinion in Pharmacology 2003; 3: 233-238. https://doi.org/10.1016/S1471-4892(03)00046-8

Joos G F, O'Connor B, Anderson S D, Chung F, Cockcroft D W, Dahlén B, et al. Indirect airway challenges. European Respiratory Journal 2003; 21: 1050-1068. https://doi.org/10.1183/09031936.03.00008403

Knapp M, Bunn W, Stave G. Adult respiratory distress syndrome from sulfuric acid fume inhalation. Southern Medical Journal 1991; 84: 1031-1033. https://doi.org/10.1097/00007611-199108000-00021

Marone G, Gentile M, Petraroli A, De Rosa N, Triggiani M. Histamine-induced activation of human lung macrophages. International Archives of Allergy and Immunology 2001;

124: 249-252. https://doi.org/10.1159/000053725

Martin J, Duguet A, Eidelman D. The contribution of airway smooth muscle to airway narrowing and airway hyperresponsiveness in disease. European Respiratory Journal 2000; 16: 349-354. https://doi.org/10.1034/j.1399-3003.2000.16b25.x

McFadden Jr E, Gilbert I A. Exercise-induced asthma. New England Journal of Medicine 1994; 330: 1362-1367. https://doi.org/10.1056/NEJM199405123301907

Niranjan R, Thakur A K. The toxicological mechanisms of environmental soot (black carbon) and carbon black: focus on oxidative stress and inflammatory pathways. Frontiers in Immunology 2017; 8: 763. https://doi.org/10.3389/fimmu.2017.00763

Parsons J P, Mastronarde J G. Exercise-induced bronchoconstriction in athletes. Chest 2005; 128: 3966-3974. https://doi.org/10.1016/S0012-3692(15)49641-2

Pauwels R A, Buist A S, Calverley P M, Jenkins C R, Hurd S S. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. American journal of respiratory and critical care medicine 2001; 163: 1256-1276. https://doi.org/10.1164/ajrccm.163.5.2101039

Pogson Z E, Antoniak M D, Pacey S J, Lewis S A, Britton J R, Fogarty A W. Does a low sodium diet improve asthma control? A randomized controlled trial. American Journal of Respiratory and Critical Care Medicine 2008; 178: 132-138. https://doi.org/10.1164/rccm.200802-287OC

Rafferty P, Beasley R, Holgate S T. The contribution of histamine to immediate bronchoconstriction provoked by inhaled allergen and adenosine 5'monophosphate in atopic asthma. American Review of Respiratory Disease 1987; 136: 369-373. https://doi.org/10.1164/ajrccm/136.2.369

Randolph C. An update on exercise-induced bronchoconstriction with and without asthma. Current Allergy and Asthma Reports 2009; 9: 433-438. https://doi.org/10.1007/s11882-009-0064-8

Ro C. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. American Journal of Respiratory and Critical Care Medicine 2000; 161: 309-329. https://doi.org/10.1164/ajrccm.161.1.ats11-99

Rodrigues M T, Fiterman-Molinari D, Barreto S S M, Fiterman J. The role of the FEF50%/0.5 FVC ratio in the diagnosis of obstructive lung diseases. Jornal Brasileiro De Pneumologia 2010; 36: 44-50. https://doi.org/10.1590/S1806-37132010000100009

Rodwell L, Anderson S, Seale J. Inhaled steroids modify bronchial responses to hyperosmolar saline. European Respiratory Journal 1992; 5: 953-962. https://doi.org/10.1183/09031936.93.05080953

Rundell K W, Jenkinson D M. Exercise-induced bronchospasm in the elite athlete. Sports Medicine 2002; 32: 583-600. https://doi.org/10.2165/00007256-200232090-00004

Rundell K W, Wilber R L, Szmedra L, Jenkinson D M, Mayers L B, Im J. Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. Medicine and Science in Sports and Exercise 2000; 32: 309-316. https://doi.org/10.1097/00005768-200002000-00010

Slovin E. Slovin's formula for sampling technique. Retrieved July 21, 2021. Journal 1960.

Sterk P J, Fabbri L M, Quanjer P H, Cockcroft D W, O'Byrne P M, Anderson S D, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. European Respiratory Journal 1993; 16: 53-83. https://doi.org/10.1183/09041950.053s1693

Svedahl S, Svendsen K, Qvenild T, Sjaastad A K, Hilt B. Short term exposure to cooking fumes and pulmonary function. Journal of Occupational Medicine and Toxicology 2009; 4: 1-8. https://doi.org/10.1186/1745-6673-4-9

TsangKW T. Bronchiectasis; notanorphandisease intheEast. The International Journal of Tuberculosis and Lung Disease 2004; 8: 691-702.

Van der lende R. Long-term variability of bronchial responsiveness to histamine in a random population sample of adults. American Review of Respiratory Disease 1993; 148: 944-949. https://doi.org/10.1164/ajrccm/148.4_Pt_1.944

Van Schoor J, Joos G, Pauwels R. Indirect bronchial hyperresponsiveness in asthma: mechanisms, pharmacology and implications for clinical research. European Respiratory Journal 2000; 16: 514-533. https://doi.org/10.1034/j.1399-3003.2000.016003514.x

Vianna E O, Boaventura L C, Terra-Filho J, Nakama G Y, Martinez J A, Martin R J. Morning-to-evening variation in exercise-induced bronchospasm. Journal of Allergy and Clinical Immunology 2002; 110: 236-240. https://doi.org/10.1067/mai.2002.125981