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INVESTIGATING THE ASSOCIATION BETWEEN AIRWAY HYPERREACTIVITY AND BRONCHOCONSTRICTOR RESPONSE TO NASAL COLD RECEPTOR STIMULATION IN ASTHMATIC PATIENTS: THE INFLUENCE OF RHINITIS SYMPTOMS

Naheed Akhtar[1]*, Rana Zain Raza[2], Muhammad Saleem Qureshi[3], Alia Chishti[4],Tamseela Shahzadi[5]

ABSTRACT

This study explored the relationship between bronchial hyperactivity to carbachol and the reflex Broncho motor response to cold stimulation of nasal receptors and any variations between asthmatic patients with and without rhinitis symptoms. The study examined the effects of breathing in cold, dry air (-4°C) through the nose on 22 healthy individuals and 18 asthmatic patients who had bronchial hyperactivity to carbachol. In both normal and asthmatic patients (asthma with rhinitis +49%; asthma alone +40%), the nasal cold air challenge caused a significant increase in Rint (+31%), however, the increase was not statistically greater than in normal individuals. In asthmatic patients with rhinitis symptoms, the amount of the Rint rise brought on by breathing cold air via the nose was linked to carbachol sensitivity, measured by the dose that generated a 50% increase in specific airway conductance (D50). These findings imply that airway hyperreactivity is linked to an increased bronchoconstriction response to the activation of nasal cold receptors, especially when rhinitis is present.

Author Affiliations
[1]Department of Pharmaceutics, The Islamia University of Bahawalpur, Pakistan.
[2]Department of Agronomy, Faculty of Agriculture, University of Poonch Rawalakot, AJK, Pakistan.
[3]Akbar Institute of Medical Sciences Bahawalpur.
[4]Department of Eastern Medicine, Faculty of Conventional Medicine, The Islamia University of Bahawalpur, Punjab, Pakistan.
[5]Riphah International University, Islamabad, Pakistan.
Corresponding author:
naheedakhtar96@yahoo.com

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INTRODUCTION

In a previous study on healthy individuals, researchers discovered a nasopulmonary bronchoconstrictor reflex triggered by inhaling cold, dry air through the nose during normal breathing(1). The afferent arm consisted of the nasal mucosa's trigeminal afferents, whereas the efferent arm consisted of the Vagus nerve. This was established by suppressing the airway response to cold air following nasal local anesthetic or anticholinergic inhalation. MCFADDEN recently revisited the concept of a nasobronchial reflex and observed that it has re-emerged after lying dormant for some hundred years (2). However, reports of this reaction in people are frequently conflicting. Some investigations did not show the reflex, whilst others observed reflex bronchospasm after nasal irritation (3, 4). Individuals suffering from perennial allergic rhinitis and stable asthma experience a decrease in their forced expiratory volume in one second (FEV1) as a result of histamine-induced nasal obstruction (5, 6). Furthermore, the study discovered that a nasal cold challenge utilizing freon-propelled aerosol generated a considerable elevation in oscillatory resistance in asthmatic patients, regardless of whether they had undergone laryngectomy (1, 7). These findings suggest that the effects of histamine-induced nasal obstruction and cold stimulation on respiratory function are particularly pronounced in individuals with pre-existing respiratory conditions, highlighting the importance of proper management and treatment. The primary

goal of this study was to look into how cold air affects the nasopulmonary bronchoconstrictor response in people with atopic illnesses. The participants in the study were asthmatic individuals who also reported rhinitis and bronchial hyperreactivity to carbachol. We compared the degree of their airway response to cold air to that of age-appropriate, healthy individuals. We hypothesized that during nasal challenges brought on by cold air, patients with bronchial hyperreactivity to carbachol would experience a larger increase in pulmonary resistance. We also hypothesized that this connection would be increased when rhinitis symptoms were present. Therefore, this study aimed to evaluate the potential synergistic influence of these factors on the bronchoconstrictor response to cold air in individuals with atopic illness.

MATERIAL AND METHODS

Study population and research design:

The study involved a total of 40 participants, consisting of 22 healthy individuals (4 females and 18 males) and 18 asthmatic patients (7 females and 11 males) with bronchial hyperreactivity to carbachol. The healthy subjects were selected based on their non-smoker status and absence of prior symptoms of asthma, rhinitis, or other atopic conditions. Meanwhile, the asthmatic patients had stable asthma, with 8 of them also experiencing symptomatic allergic rhinitis. Notably, none of the individuals reported rhinitis symptoms during the lung function testing, which included a nasal cold challenge. No patients received any particular therapeutic drugs, such as steroids, ipratropium bromide, cromolyn, or antihistamines, for at least a month before the study to guarantee accurate results. Participants were granted written consent and fully informed of all procedures in compliance with the standards set by the Institutional Human Subjects Committee. However, they were not made aware of the purpose of the study.

The values in the study are shown as mean ± SEM. Body temperature, atmospheric pressure, and water vapour saturation (BTPS) were taken into account while adjusting the observations. Vital capacity (VC), forced expiratory volume in one second to VC (FEV1/VC), residual volume to total lung capacity (RV/TLC), specific airway conductance (sGaw), interrupting resistance (Rint), and bronchial hyperresponsiveness (BHR) are the characteristics that are taken into consideration. When comparing the baseline saw measurements of asthmatic patients and normal people, there was a significant difference (p-value < 0.05).

Table 1 shows the individuals' functional characteristics are displayed. To evaluate the alterations in airway resistance brought on by breathing in cold, dry air through the nose, we measured the baseline interrupting resistance (Rint) before the experiment. Every five minutes, the subjects were given a cold air inhalation for fifteen minutes, followed by a ten-minute recuperation period during which they breathed room air. To ensure consistent nasal stimulation between two consecutive Rint measurements during cold air inhalation, the subjects were instructed to inhale through their nose once and then twice through their mouth.

Methods

Analyzing the response of the airways to carbachol:

A dose-response curve was developed by plotting the specific airway conductance (sGaw) value from a whole-body plethysmograph against cumulative carbachol doses in the range of 100-2,000 µg on consecutive days (8). The slope of the sGaw vs. carbachol dosage relationship was used to describe reactivity, and the dose that caused a 50% increase in sGaw (D50) was used to characterize sensitivity to carbachol (9, 10). A D50 of less than 800 µg was

considered hyperreactive to carbachol in the patients. For fourteen asthmatic people, the D50 value was less than 500 µg.

Respiration variables are measured:

The identical experimental set-up from earlier studies was employed(1). Individuals were measured while they were relaxed in their seats. In every instance, patients breathed in through a two-way valve with a dead space of 5 mL, which prevented expired gas from contaminating the inspired air. The relative humidity (RH) was only 0.3% and the temperature was -5°C. The patients were required to breathe through their noses while wearing a mask with a dead space of 140 mL. The interrupting device had a throttle valve and an electromanometer to monitor mouth pressure, and the participant breathed into a grid pneumotachograph to measure rint. After two breaths, a single 100 ms occlusion was carried out at 50% of the tidal volume that had already expired. Rint was therefore consistently evaluated at mid-tidal expiratory flow. The individuals breathed in sync with a metronome at a rate of 15 breaths per minute while inhaling ambient air or controlled air. The last alteration in breathing pattern that occurred during the inhalation of cold, dry gas was the reason for these decreased mechanical distortions. It was found that breathing at room temperature or cold air did not affect the end-tidal CO2 tension, hence preventing the bronchomotor effects of mild hypocapnia. Temperatures were recorded on a voltmeter using Type K chrome-alumni thermocouples with a 0.1s time constant. Just before the two-way valve was placed, the inspired temperature was recorded three centimetres from the mask's entry. The inspiratory line of the circuit was equipped with a thermohygrometer with a time constant of three seconds. A digital voltmeter was used to measure the RH levels.

Setup to adjust the temperature and humidity of inhaled air:

As previously mentioned, a calcium chloride column was used to dry the compressed air after it was supplied into an industrial freezer at a flow rate of 30 L/min. Next, a low-resistance circuit with a copper spiral immersed in a glycol bath was used to cool the air to -5°C (1). With a four-way stopcock, it could route conditioned air to either the room or the inspiratory circuit. The pressurized air circuits' stopcock was turned on, and the mask level fluctuated by less than 1 cmH2O.

Interpretation:

After validating the normality of data distribution, one-way repeated measurement analysis of variance (ANOVA) was used to assess changes in the effects of several experimental conditions on the same set of subjects. This was done by looking at the changes in each subject individually. The post-multiple comparison test was employed when Dunnett's method revealed a noticeable variation ($p < 0.05$) within the boundaries of the current experimental setup. The mean change in Rint was compared between healthy participants and patients, Asthmatic Patients alone or with clinical symptoms of rhinitis, and healthy subjects and patients using the student's t-test.

RESULTS

According to Table 1, sGaw was substantially lower in patients than in control persons. Although this was not the case for Rint values, it is generally recognised that this approach has lower sensitivity than conventional methods for identifying bronchoconstriction (11). There were no discernible changes between patients with and without rhinitis. Figure 1 demonstrates that during the nasal cold air challenge, Rint considerably increased in healthy participants (+31%; $p<0.01$). Throughout the

test, there was a minor, insignificant trend for the airway reaction to respond.

The starting point Five minutes after the conclusion of the cold air test, the Rint value was reliably retrieved. The airway response to a challenge involving cold air entering through the nose was examined independently in patients with asthma, regardless of whether they had symptoms of rhinitis. Both asthma patient groups (asthma with rhinitis +49%; asthma alone +40%) seemed to have higher levels of cold air-induced rint, however, the differences were not appreciably greater than in normal controls.

(Fig.1) shows the absolute values of interrupting resistance increases (∆Rint) in normal individuals and asthmatic patients with or without symptoms of rhinitis. The measurements were taken in response to nasal inhalation of cold, dry air (-5°C) and during the first 10 minutes of the recovery period. Significant increases in Rint were observed in all three groups of subjects, with a statistical significance of $p<0.01$. Although asthmatic patients displayed a tendency towards a greater airway response to cold air, the differences between them and the healthy volunteers were not statistically significant (Figure 2). A study looked at the association between two variables: bronchial sensitivity to carbachol (defined as the dose that causes a 50% increase in specific airway conductance (D50)) and interrupting resistance (∆Rint) during nasal cold dry air intake. The study concentrated on two subsets of asthma patients: those who only had asthma and those who also had rhinitis. Only asthmatic individuals with rhinitis symptoms showed a significant linear connection ($r=-0.830$) with a p-value < 0.01. The equation of the regression line for this group of patients is ∆Rint=3.09–4.73. D50, meaning that as D50 (bronchial sensitivity to carbachol) increases, the ∆Rint (increase in interrupting resistance) decreases. However, in the group of asthmatic patients without rhinitis, the correlation between ∆Rint and D50 was not significant, as indicated by the lower correlation coefficient ($r=-0.520$) and a non-significant p-value ($p=0.15$). The dotted lines on the graph represent the 95% confidence intervals for the regression lines, indicating the range of values within which the real correlation coefficient is most likely to occur.

DISCUSSION

The current findings support the observations that normal individuals have a nasopulmonary bronchoconstrictor reaction to cold, dry air (1). The airway sensitivity to breathing in cold, dry air was noticeable and worsened in this group of asthmatic individuals. Asthmatics with rhinitis demonstrated similar bronchoconstrictor responses to nasal cold air exposures as those with asthma alone. The most susceptible to carbachol showed an enhanced bronchomotor response to nasal inhalation of cold air, and there was a significant correlation between individual carbachol sensitivity and cold air-induced Rint alterations (D 50). Nevertheless, only asthmatic individuals with a history of recurrent rhinitis episodes showed this correlation. The interrupter technique exhibited inferior sensitivity in identifying bronchoconstriction compared to the measurement of sGaw utilizing a body plethysmograph (11). However, in our experimental design, using a body plethysmograph would require suspending the nose intake of cold air for an extended length of time, resulting in an adjustment of the cold-induced airway response during the interval of sGaw measurement. The current study reveals that inhaling cold air through the nose causes changes in airway resistance due to the activation of the trigeminal nasal afferent reflex. In healthy people, local anaesthetic of the nasal mucosa reliably reversed changes in Rint,

indicating that chilling the airway mucosa directly is improbable (1, 12). The direct cooling of the airway mucosa is not possible due to certain limitations. The activation of cold receptors in the skin can lead to bronchospasm (13, 14). However, the current method of nasal inhalation of cold air does not engage this reflex route since the airway response reduces after the application of local anaesthetic to the solitary nasal mucosa, as established by these studies. The capacity of the upper airway to condition and regulate the temperature of inhaled air was overpowered when participants hyperventilated freezing air (-19°C) through their oral cavity, which resulted in an instant cooling effect on the tracheal mucosa. Consequently, the observed increase in airway resistance during normal nasal breathing of moderately cold air (-5°C) could be the outcome of a reflex action stimulated by the activation of cold-responsive nerve endings in the upper respiratory tract (14). Cold receptors have been discovered in animals' larynx, upper trachea, and nose (15, 16), as well as in humans' noses and hypothesized in the oropharynx (1, 17). Upper airway constriction in response to trigeminal afferent activation since prior anticholinergic inhalation eliminated Rint changes triggered by nasal cold challenge (18). Scientists ascertained that there was no correlation between the reduction in FEV1 triggered by histamine nasal stimulation and the sensitivity of bronchial smooth muscles to histamine(19). In healthy people, the nasopulmonary tissues' bronchoconstrictive response to a cold air stimulus was minimal or nonexistent, but it was noticeable in asthmatic patients (7). The present results are only partly consistent with the study of NOLTE and BERGER (7), as we also observed a substantial (+30%) rise in airway obstruction in healthy subjects when subjected to cold air. The dissimilarity in the magnitude of airway responses observed in the two studies could be ascribed to the dissimilarity in the duration of nasal cooling, which persisted for 15 minutes in the present study, while NOLTE and BERGER utilized a solitary application of freon-propelled aerosol consisting of fluorchlor and methane or ethane in their investigation (7). Our findings imply that the airway reaction to nasal cold air provocation was particularly discernible in specific asthmatic patients who simultaneously exhibited rhinitis symptoms. We have a dearth of explanation for the mechanism of this association because the assessment of nasal resistance was not conducted on the current cohort, thereby precluding analysis of the nasal reaction to inhaling cold, arid air. Nonetheless, none of the participants experienced nasal congestion symptoms during the cold air test, and some individuals even noted an improvement in their ability to inhale through their noses. The main point of contention is that the increased susceptibility of the airway smooth muscle to bronchoconstrictor medications frequently causes an amplified contractile response to any vagally mediated responses, including those evoked by the activation of cold receptors in the airways. As a result, the cold-induced, vagally-mediated bronchospasm was considerably larger in rabbits that were sensitized to bovine serum albumin and demonstrated bronchial hyperresponsiveness to histamine than in nonsensitized animals (20). Our research demonstrated that exogenous protein sensitization modified the intrinsic characteristics of tracheal smooth muscle, leading to an enhanced contractile response to vagal motor control stimulation in all its manifestations, including phenyldiguanide-induced bronchopulmonary C-fibres. The heightened bronchoconstrictor response that asthmatics experience in cold air is probably caused by this mechanism. Recent

findings reveal that in patients with rhinitis who have asthma and are sensitive to carbachol (defined as the quantity that causes a 50% increase in a specific airway conductance), the nasopulmonary region's bronchoconstrictive response to breathing in dry, cold air was significantly increased. In some individuals, the escalation in airway constriction could attain 3–4.6 cmH2O·L-1·s, along with a sensation of shortness of breath. This test, which involves inhaling chilly air through the nose, can be advised as a predictive tool for assessing cold sensitivity in asthmatic patients who intend to ski or participate in other winter activities.

CONFLICT OF INTEREST:

The Authors have no Conflict of Interest.

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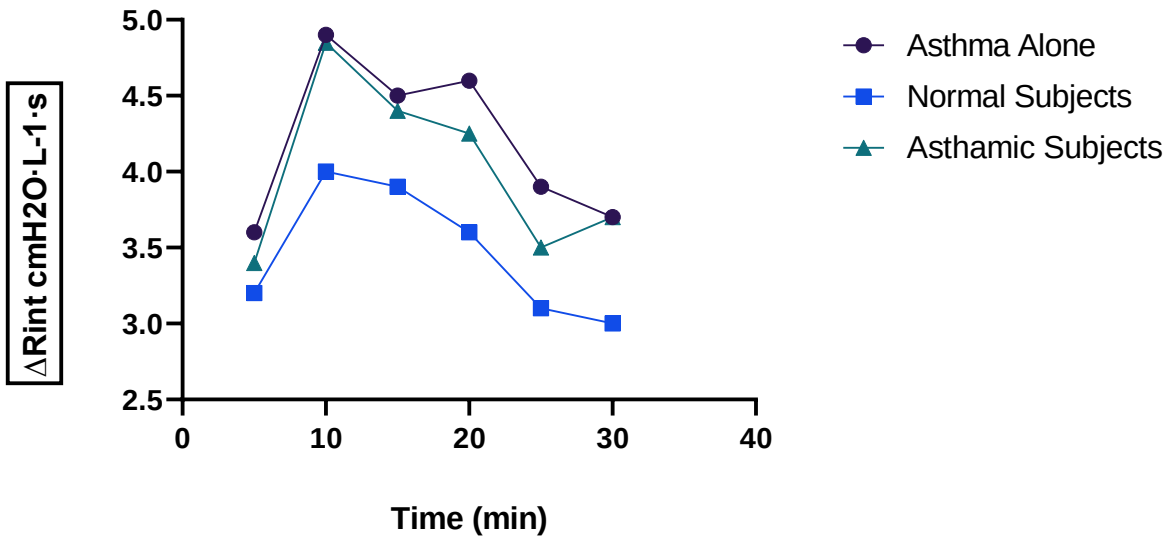
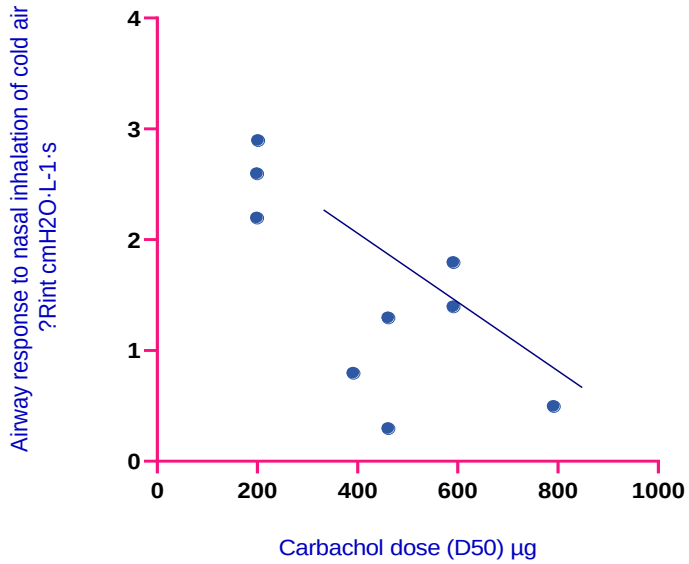
Table 1: Morphology and pulmonary function of the subjects examined

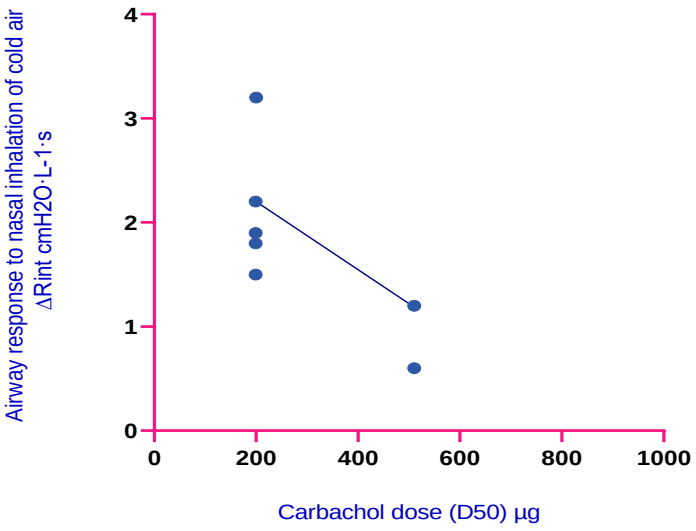
Subjects	Height (cm)	Weight (kg)	Age (years)	Vital Capacity (VC)	FEV1/VC (%)	RV/TLC (%)	Rint cmH2O·L^{-1}·s	Saw cmH2O^{-1}·s^{-1}
Normal(n=22)	172	71	43	5.00	83	33	3.2	0.173
Bronchial hyperresponsiveness (n=18)	168	74	37	4.5	81	34	3.7	0.126

Table 2: Airway Reaction with Time

Airway Reaction	Time (min)
+31%	5
+26%	10
+16%	15




Airway response to nasal inhalation of cold air
?Rint cmH2O·L-1·s
4
3
2
1
0
0
200
400
600
800
1000
Carbachol dose (D50) µg


Airway response to nasal inhalation of cold air
ΔRint cmH2O·L-1·s
4
3
2
1
0
0
200
400
600
800
1000
Carbachol dose (D50) µg