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Identification of Patients with Reactive Airways at Ambient Temperatures

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Abstract

Background: *This study aimed to characterize respiratory resistance values of reactive and non-reactive airways. Being able to test for reactivity can be beneficial in the medical realm to prescreen patients for respiratory diseases. Reactive airways are airways that narrow due to an external stimulation, which cause a patient to wheeze. The symptoms vary and can be like those of asthma. They are of great interest because patients with reactive airways are exposed to a risk of long-term airway damage.*

Methods: *Thirty subjects were asked to breathe ambient temperature room air at 21° Celsius, while breathing through an airflow perturbation device (APD). The APD is a new instrument that rapidly and non-invasively measures respiratory resistance. Respiratory resistance values were examined among subjects at 60 second intervals for a total of 5 measurements.*

Results: *Of 30 subjects between ages 18 to 54 years, 9 (30%) were identified to have reactive airways with statistical significance of $p \leq 0.05$.*

Conclusion: *Testing respiratory resistance using the APD could be a prescreening for reactive airways in exercised-induced asthma in cooler temperatures.*

Keywords: *Respiratory Resistance, Airways, Exercise-Induced Asthma, Asthma*

Introduction

Globally, there are millions of people with a respiratory disorder, such as asthma, pneumonia, and bronchitis [1]. About 235 million people suffer from asthma alone [2]. Respiratory resistance is a key measure of pulmonary function, and is defined as the respiratory pressure gradient divided by the airflow. Higher resistance values usually result in more difficulty breathing. There are three determinants of respiratory resistance including the components of airways, lung tissue, and chest wall [3]. In addition, respiratory resistances can be different for both inhalation and exhalation.

A common respiratory disorder is an exercise- and cold-induced asthma, where inflammation and production of mucus in the airways [4], leads to narrowing of the airway and a subsequent increase in airway resistance [5]. This respiratory illness can be triggered by hyperventilation in cold, dry air. The narrowing of the airway is a result of a reactive airway to external factors. Breathing in colder and drier air quickly causes the loss of heat and/or water from the lungs. Cooling of the airways likely causes vasoconstriction and reactive hyperemia of the bronchial microcirculation, resulting in airway narrowing during exercise [6]. Many factors trigger or exacerbate symptoms among affected individuals: cold air, dry air, respiratory infections, hyperventilation, airborne irritants and extended periods of deep breathing. Symptoms can include, but are not limited to, shortness of breath, cough, sore throat, tightness in chest, and wheezing [7].

Exercise-induced asthma was defined as a fall in peak expiratory flow, PEV [8]. They reported a prevalence of exercise-induced asthma to be 42% [8]. Other studies conducted showed its prevalence to be up to 90 percent [9-12].

Exercise-induced asthma can be clinically diagnosed with exercise challenges, pulmonary function testing, imaging studies, and laryngoscopy [13, 14]. The sensitivity of airways reactivity can be determined directly through a transient narrowing of the airways during a methacholine challenge test, which exposes patients to stepwise elevated doses of the bronchoconstrictor drug methacholine in the inspired air [15]. Other tests to evaluate the presence of exercise-induced asthma include re-creating an environment where exercise-induced asthma would result, such as field exercise or running on a treadmill. These tests increase intensity as time elapses. Other indirect tests could include a voluntary hyperpnea challenge test or osmotic challenge test: the voluntary hyperpnea challenge test reproduces exercise-induced asthma by hyperventilation of dry inhaled air, and the osmotic challenge test involves elevating doses in the inhalation air of a dry powder mannitol or hypertonic saline [15]. Many of these are relatively time-consuming and expensive diagnostic tests.

Testing with the airflow perturbation device (APD) may be able to determine airway sensitivity to cool or dry air more quickly and inexpensively than traditional methods. The APD is an instrument used to measure respiratory resistance noninvasively by calculating and computing the sum of pulmonary and chest wall resistances [3]. This device is small, lightweight, and portable, making it easily accessible for use in any clinical setting [3]. The APD is composed of many parts, including a pneumotachograph, two differential pressure transducers, a segmented wheel, motor, and a signal conditioning circuit [16]. Subjects hold this device while they breathe normally through a disposable mouthpiece. A nose clip may be used to direct the respiratory airflow through the mouth [3]. The APD separately measures inhalation and exhalation respiratory resistance values, but also outputs an overall average value [1]. The APD can be used to monitor resistance changes as they occur. Otherwise, respiratory resistance readings are usually averaged over a time span of about a minute. Separate inhalation and exhalation values can provide useful diagnostic information related to specific respiratory diseases [17].

The objective of this study was to establish that patients with airways sensitive to cool ambient air can be detected using the APD in serial fashion, with the possibility that this test could be used as a simple means to prescreen for exercise-induced asthma.

Methods

Thirty subjects took part in this study. Subjects were eighteen years of age or older, and provided written informed consent. The present study was approved by the University of Maryland Institutional Review Board. Subjects completed a self-administered questionnaire of demographics and medical history: age, gender, height, weight, and whether the subject has asthma, allergies, and difficulty breathing in colder temperature air. Subjects were then given a nose clip and clean mouthpiece. While they wore the nose clip, the mouthpiece was placed onto the APD device. Subjects were asked to sit upright and hold the APD device perpendicularly in their right hand. They were instructed to breathe normally into the device with their tongues kept away from the opening of the mouthpiece.

Ambient room temperature was measured in the laboratory at about 21° Celsius. Subjects were tested for respiratory resistance once per minute for five total measurements. The respiratory resistance values for inhalation, exhalation, and average displayed by the APD at each measurement were recorded. To minimize variability due to the instrument itself, all subjects were tested using the same APD device [18].

Statistical Analysis

Slopes of resistances with time were determined by linear regression using all five measurement values. Statistics were used to test if resistance variations with time were different from zero. A t-statistic was calculated to test for statistical significance of the slopes with time for inhalation, exhalation, and average resistances for each subject. If a p-value was ≤ 0.05, the slope value was found to be statistically significantly different from a slope of zero. We could conclude, in that case, that the subject with that slope of resistance with time likely had reactive, or temperature-sensitive, airways. If the p-value was > 0.05, the subject had non-reactive airways.

Results

The demographics and results of all thirty subjects are shown in Table 1. The subjects varied in age, gender, height and weight. Eighty percent of the subjects were between 18-21 years of age. There were 57% females and 43% males. Resistance values (in units of cm H_2O·sec/L, or cm H_2O/Lps) were calculated as the average of all resistance measurements on all subjects. As expected from previous studies [1, 17], exhalation resistances were found to be greater than resistances during inhalation.

Table 1. *Subject Demographics and Results for Thirty Subjects*

Characteristic	Mean ± Standard Deviation	Range
Sex	17F, 13M	
Age	22.4 ± 8.41 years	18 to 54 years
Height	158 ± 10.2 cm	153 to 186 cm
Weight	65.6 ± 13.5 kg	43.9 to 94.3 kg
Inhalation Resistance	3.50 ± 0.63 cmH_2O/Lps	1.60 to 5.38 cmH_2O/Lps
Exhalation Resistance	4.27 ± 1.01 cmH_2O/Lps	2.95 to 8.34 cmH_2O/Lps
Average Resistance	3.89 ± 0.601 cmH_2O/Lps	2.84 to 5.77 cmH_2O/Lps

Seventeen percent of the subjects reported to have asthma (Table 2). Forty-three percent of the subjects reported to have allergies. Twenty-three percent of the subjects self-reported to have difficulty breathing in cooler air temperature.

Individual slope values (rates of change of respiratory resistance, in units of cm H_2O/L) for each subject are found in Table 2. Data for each subject's resistance slopes include five measurements of respiratory resistance at sixty second intervals for inhalation, exhalation, and average. Statistical significances are denoted by asterisks after resistance rate values. All significant slopes were positive, denoting that resistances increased as the subjects continued to breathe ambient air. There were several negative resistance slopes, but none of these reached statistical significance different from zero.

Table 2. *Respiratory Resistance Rates (cmH_2O/L)*

Subject	Inhalation Slope	Exhalation Slope	Average Slope
1	0.000333*	0.000417*	0.000375*
2[1]	-3.33E-05	-3.33E-05	-3.33E-05
3[3]	0.0001167	0.000250	0.000183
4[1,3]	0.000367*	0.000283*	0.000325*
5[1,3]	0.000167*	0.000183	0.000175
6[1,2,3]	1.67E-05	-1.67E-05	0.000
7	-8.33E-05	-3.33E-05	-5.83E-05
8	5.00E-05	-1.67E-05	1.67E-05
9[2,3]	8.33E-05	1.00E-04	9.17E-05
10[1,2]	8.33E-05	0.000150*	0.000117*
11	7.40E-19	0.000183	9.17E-05
12[1,2]	0.000633*	0.000450*	0.000547*
13	1.67E-05	0.000450	0.000233
14	-0.000383	0.000150	-0.000117
15[1]	0.000650*	0.000550*	0.000600*
16	-6.67E-05	0.000217	7.50E-05
17[1,3]	-0.000100	0.000233	6.67E-05
18	-3.33E-05	-5.00E-05	-4.17E-05
19	0.000133	0.000200	0.000167
20	0.000217	1.67E-05	0.000117
21[1]	-0.000133	-0.000350	-0.000242
22[3]	0.000483*	0.000467*	0.000475*
23	0.000300	0.000233	0.000267
24[1]	0.0001167	0.00178	0.000950
25[1]	0.000167	8.33E-05	0.000125
26	0.000117	0.000117	0.000117
27	-6.67E-05	8.33E-05	8.33E-06
28	3.33E-05	8.33E-05	5.83E-05
29[1]	0.000750*	0.000700*	0.000725*
30[1,2]	0.000367*	0.000250*	0.000308*

*subjects with reactive airways, statistical significance $p \leq 0.05$

[1]subjects with allergies, [2]subjects with asthma, [3]subjects with difficulty breathing in cooler temperature air

Figures 1-4 show the respiratory resistance values over time for four different subjects. Using a t-test, data from subject #20, shown in Figure 1, proved to have no statistically significant slope different from zero. Thus, that subject was said to have non-reactive airways. Data from subject #1, shown in Figure 2, proved to have slopes statistically significantly different from zero for both inhalation and exhalation. Thus, those airways were designated as reactive. In Figure 3 are data from subject #5 with partially reactive airways. Only the inhalation slope proved to be statistically significantly different from zero. Figure 4 shows data from subject #10, where only the exhalation and average slope values proved to be statistically significant for reactivity.

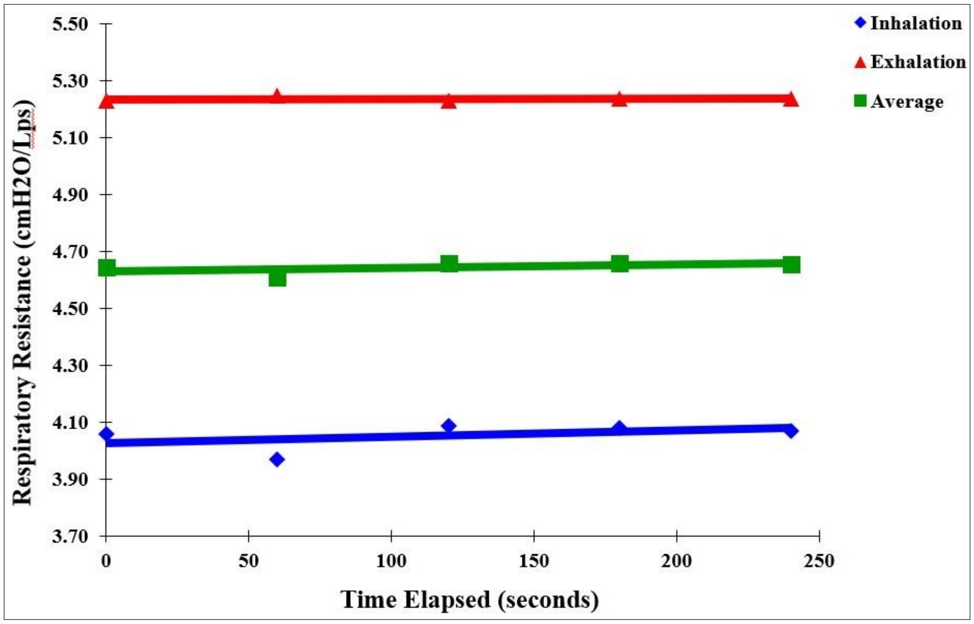

Fig 1. *Respiratory resistance values over time for subject #20. There are no statistically significant differences in respiratory resistance slopes to show any reactivity in this subject's airways.*

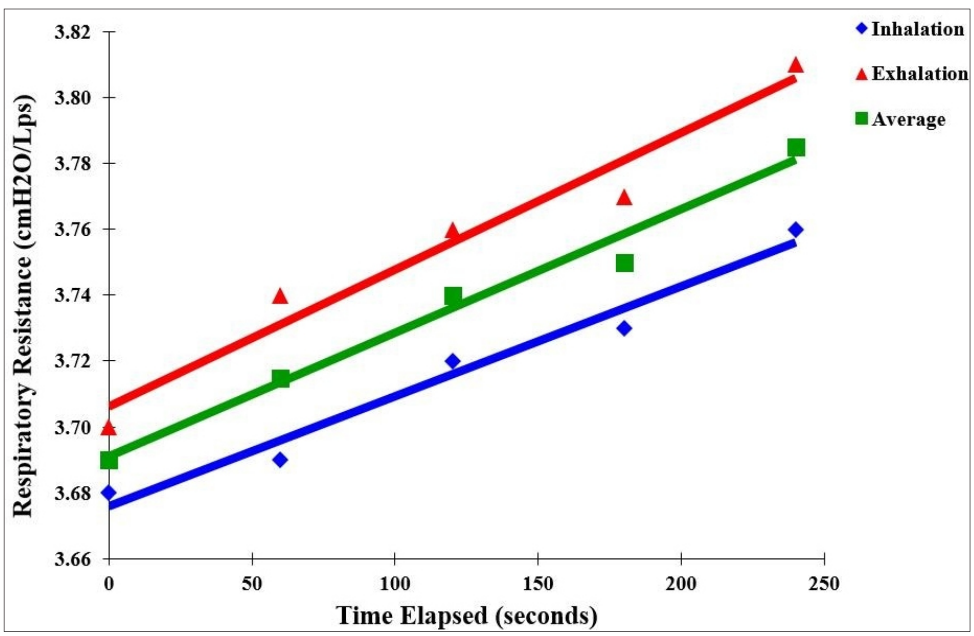

Fig 2. *Respiratory resistance values over time for subject #1. There are statistically significant differences in respiratory resistance slopes, which indicate reactivity in this subject's airways in both inhalation and exhalation directions.*

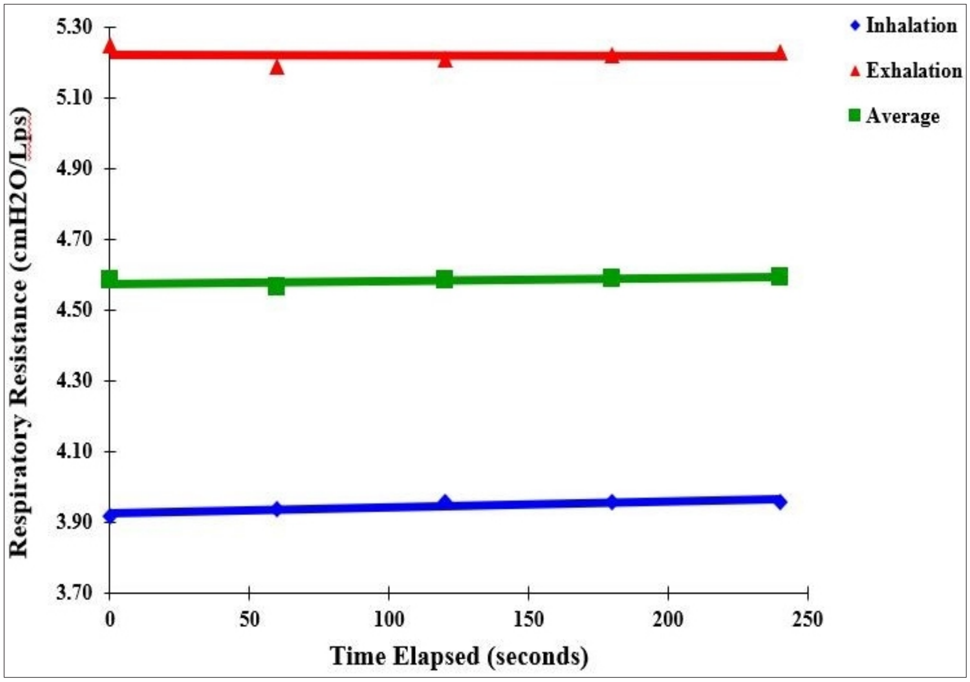

Fig 3. *Respiratory resistance values over time for subject #5. There are no statistically significant differences in average or exhalation respiratory resistance slopes. However, there is a statistically significant difference in inhalation respiratory resistance slope, which indicates reactivity in this subject's airways during inhalation. At least one other subject (#10) demonstrated statistically significant slopes for exhalation and average respiratory resistance, but not for inhalation.*

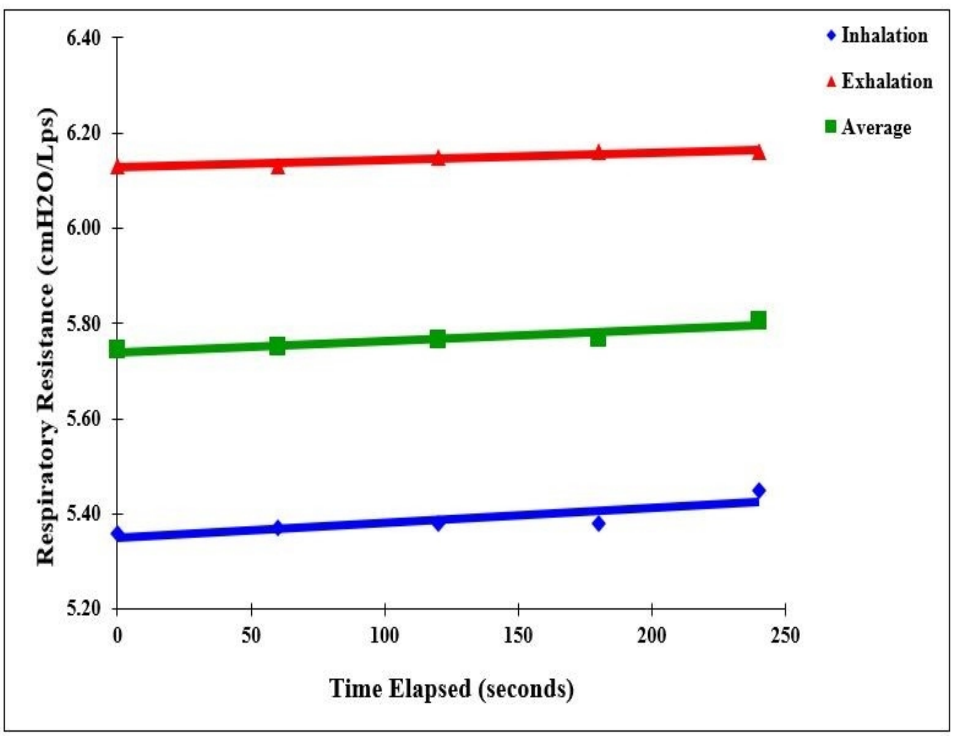

Fig 4. *Respiratory resistance values over time for subject #10. There is no statistically significant difference in the inhalation respiratory resistance slope. However, there are statistically significant differences in average and exhalation respiratory resistance slopes, which indicate reactivity in this subject's airways during exhalation.*

Thirty percent of subjects proved to have statistically significant reactive airways for at least one inhalation or exhalation rate of resistance change with time. Nine subjects, or 26%, were determined to have reactive airways during inhalation. One of these subjects exhibited significance during inhalation only, but not for exhalation. For each statistically significant rate of change during exhalation, the average resistance change was also found to be significant. Seventy percent of subjects showed no statistically significant difference, leading to the conclusion that they had non-reactive airways.

Discussion

Results from this experiment on thirty subjects have demonstrated that patterns of resistance change with time can be obtained simply using the APD. Some subjects were found to have resistance values that changed over time, and the cause of these changes was assumed to be temperature sensitivity of the airways.

Air is not conditioned as much when breathing through the APD as it would be if the mouth were partially closed, or if nasal breathing occurred. Lack of conditioning of the air would allow drier and somewhat cooler air to reach the airways directly and to trigger partial airway closure. Thus, even moderate room temperatures could produce the airway reactions seen here. Out of thirty subjects, nine of them proved to have statistically significant rates of change of resistances with time. Consequently, all other subjects proved to have non-reactive airways under these experimental conditions.

Subjects were asked to complete a health questionnaire where each had to report the existence of allergies, asthma, and/or whether they had difficulty breathing in cold temperatures. Upon close examination of these designations in Table 2, it is difficult to see any pattern between self-reported respiratory conditions and statistically significant resistance changes. For instance, of the seven subjects claiming difficulty breathing cool air, three had at least one significant slope and four did not; of the 13 subjects reported to have allergies, seven had at least one significant slope, but six did not; of the five subjects with asthma, three had at least one significant slope, and two did not.

The reasons for this lack of clear correlations between reported respiratory condition and reactive slopes may be several-fold. First, the room temperature air that was used for this study may not have been severe enough to elicit reactivity response in all subjects with the designated respiratory conditions. We were reluctant to use cooler air because of the danger of eliciting so much reaction as to cause a medical emergency. Under proper medical supervision, this test of airway reactivity might be carried out with colder ambient temperatures that give more meaningful results. Nonetheless, even with room temperature air, we were able to detect at least some airway sensitivity. If airway reactivity can be detected with room-temperature air, then testing for sensitive airways becomes that much simpler.

The other reason that there was no clear-cut agreement between reported respiratory condition and these test results is due to the vague nature of the health history questions. It wasn't clear whether the reported respiratory conditions were still problematic or how severe they were, if still present. So, further work with more explicit information might yield more consistent results.

There was one subject (#5) with a reactive airway in the inhalation direction who did not exhibit reactivity during exhalation. This is an intriguing result, because the subject had not reported asthma, but did have allergies and cool-air breathing difficulty. We have used the APD as a diagnostic tool for Paradoxical Vocal Fold Motion Disorder (PVFMD, a form of laryngeal dyskinesia manifested during exercise and often mistakenly diagnosed as asthma [19]). Inhalation resistance for this condition increases due to adduction of the vocal cords during heavy breathing. The APD can pick up this condition because it separates inhalation resistance from exhalation resistance during noninvasive breathing. The diagnostic standard for PVFMD is a laryngoscope inserted into the throat of a heavily-breathing athlete. Our subject #5 may have had this condition.

There is a large amount of literature about the treatment of allergic rhinitis and sinusitis [20, 21, 22], and nasal allergic reactions to seasonal airborne allergens cause many difficulties for those who suffer from these conditions. However, these conditions have different causes than temperature-sensitive airways reactivity, and are not likely to be able to be diagnosed with the methods used in this research. The selectivity of the airway challenge investigated in this research is a strength of this method, and can point directly to a specific cause for nasal breathing difficulty.

Our results imply the process used here involving measuring respiratory resistances over time using an APD may be a way to prescreen for reactive airways. In the medical realm, it is possible that if a patient has reactive airways, they could be a possible candidate for exercise-induced asthma in cooler air temperatures.

Conclusion

Our data suggests that the APD may be a useful prescreening tool to identify reactive airways in exercise-induced asthma in cooler temperatures. The APD could distinguish whether a patient has reactive inhalation airways or reactive exhalation airways. Additional data collection will have to be performed to determine if specific cooler air temperatures have different effects on respiratory resistance values determined by an APD.

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