Perception of Inspiratory Resistive Loads in Asthmatic Children with Attention Deficit Disorder

Kathleen L. Davenport, Steven M. Julius and Paul W. Davenport

Departments of Pediatrics and Physiological Sciences, University of Florida, Gainesville, FL.

Abstract: Magnitude estimation (ME) of inspiratory resistive (R) loads has been studied in asthmatic children. Some children have been reported to be unable to perform the perception task. One reason some children may be unable to perform the ME task is Attention Deficit Disorder (ADD) or Attention Deficit Hyperactivity Disorder (ADHD). The aim of this study was to determine if asthmatic patients with ADD/ADHD have a perceptual and/or attention deficit in the ME of graded inspiratory R loads.

Methods: Asthmatic children aged 11–18 years were classified into ADD/ADHD and asthma control groups. Perception of extrinsic loads was assessed by handgrip ME of inspiratory R loads. A methacholine challenge was performed and the PC_{20} for each subject determined.

Results: There was no significant difference between asthma control and ADD/ADHD groups in the group mean for the slope of ME-R load slopes. The ADD/ADHD subjects had significantly greater variability in ME of R loads.

Conclusions: Asthmatic children with ADD/ADHD do not have an impaired perception of extrinsic respiratory loads but do have difficulty attending to the perceptual task. Difficulties in their asthma management may be due to their attention deficit and not their symptom perception.

Keywords: respiratory sensation, psychophysics, inspiratory load, resistive load, load compensation

Introduction

Attention-deficit disorder (ADD) or attention-deficit hyperactivity disorder (ADHD) is the most commonly treated emotional, cognitive and behavioral disorder in children [Wilens et al. 2002]. The symptoms of ADD/ADHD include hyperactivity, poor attention at school, excessive energy and/or inability to pay attention to any given task [Hill, 1998]. Those suffering from ADD/ADHD are most symptomatic in situations requiring sustained attention. The origins of this ailment are uncertain, but it is widely accepted that heredity plays an important role [Wilens et al. 2002; Spencer, 2002].

Asthma is another disease prevalent in children. To control and/or prevent an asthma attack, it is important for the patient to attend to warning signs of bronchoconstriction and be compliant with their prescribed medication regimen. Failure to do so is a primary cause of severe attacks. Noncompliance can be the result of many factors, including difficulty in attending to asthma symptoms or the task of following the prescribed medication regime [Julius et al. 2002].

The measurement of respiratory mechanical load sensation requires subjects to perform respiratory behavioral tasks similar to asthma symptom perception. This procedure has been used to study the perceptual sensitivity of asthmatic patients to inspiratory loads of varying magnitudes and types [Julius et al. 2002; Kifle et al. 1997; Davenport and Kifle, 2001]. Subjects receive instructions on the behavioral task and often a practice session. This process allows the subjects to learn the respiratory perception behavior and become familiar with the mechanical load sensation. The subjects then perform the respiratory load test without further prompting. In order to successfully perform the load test, the subject must attend to the load, sense the magnitude of the load and then provide an estimate of their sense of load magnitude using scaling techniques. There are many reasons a subject may have poor perception of a respiratory load, including difficulty in perceiving respiratory loads and difficulty attending to the respiratory task.

Correspondence: Dr. Paul W. Davenport, Department of Physiological Sciences, Box 100144, HSC University of Florida, Gainesville, FL32610. Tel: (352) 392-4700, ext. 3825; Fax: (352) 392-5145;
Email: davenportp@mail.vetmed.ufl.edu

Previous studies have examined the effects of ADD/ADHD on ability to attend to behavioral tasks [Antrop et al. 2000; Borger and van der Meere, 2000; Cepeda et al. 2000]. These studies have found that patients suffering from ADD/ADHD have decreased ability to attend to a task. Additionally, it has been shown that patients with asthma have greater inaccuracy in perception of respiratory loads during periods of decreased attention [Meek, 2000]. It has also been reported that 12.1% of asthmatic children have ADD/ADHD comorbidity [Blackman and Gurka, 2007]. Previous studies have also examined asthmatic patients' ability to perceive a respiratory load [Julius et al. 2002; Kifle et al. 1997; Davenport and Kifle, 2001]. It was reported that a sub group of asthmatic patients (who did not have ADD/ADHD) had a decreased ability to perceive respiratory loads [Kifle et al. 1997]. Asthma and ADD/ADHD occurs infrequently in the same patients and are transmitted separately [Biederman et al. 1994; Blackman and Gurka, 2007]. However, no study has examined perception of breathing in these unique patients with both ADD/ADHD and asthma. In the present study, we hypothesized that asthmatic patients who have ADD/ADHD will become inattentive to the procedure and their magnitude estimation of inspiratory resistive loads will be reduced and demonstrate greater response variability.

Materials and Methods

Subjects

Subjects were 11–18 years of age. All subjects were diagnosed with asthma for a minimum of one year per medical record and were on a daily medication that controlled their asthma (Tables 1 and 2). All subjects were patients of the Pediatric Pulmonary Division, University of Florida and were recruited consecutively during the study's one-year accrual period. The study was approved by the University of Florida Institutional Review Board.

Two groups of subjects were studied: patients with only asthma and patients with both ADD/ADHD and asthma. Subjects with ADD/ADHD and asthma were required to fulfill all the above criteria for subjects with only asthma. The diagnosis of ADD/ADHD had been made by a pediatric clinician at the University of Florida, as indicated in medical records. A pulmonary function test was administered before testing began and all subjects had a baseline FEV_1 and FVC greater than or equal to 70% of predicted.

Inspiratory R load magnitude estimation

Perception of inspiratory R loads was determined using magnitude estimation of load magnitude with handgrip response. The subject was seated in a sound isolated chamber, separated from the investigator and the experimental apparatus. The subject's nose was clamped and they respired through a mouthpiece connected to a non-rebreathing valve (Hans Rudolph, Kansas City, MO).

The R loads were placed in series in a loading manifold with stoppered ports between the resistances. The loading manifold was connected to a pneumotachograph, connected by reinforced tubing on the inspiratory port of the non-rebreathing valve. Mouth pressure (P_M) was recorded from a port in the center of the non-rebreathing valve. Inspiratory airflow (V'_I) was recorded with the pneumotachograph. The V'_I was integrated to obtain the inspired volume (V_I). The P_M, V_I and V'_I were recorded on a computer polygraph (Chart, ADInstruments, Inc.). The V'_I was also displayed on an oscilloscope placed in front of the subject. The peak V'_I during normal, tidal breathing was determined and displayed as a horizontal line on the oscilloscope. The subject inspired to this target V' line with each loaded and unloaded breath.

Handgrip magnitude was used by the subjects to estimate the magnitude of the R load. Subjects were asked to squeeze a handgrip placed in their dominant hand. All handgrip magnitude estimations were expressed as percentage of the maximum grip (mean of the three efforts).

Resistances were selected by removing a stopper and allowing the subject to inspire through the selected port. The presentation of six resistive load magnitudes (1.64, 2.48, 3.26, 6.95, 11.46, 20.48 cm H_2O/L/s) and no-load control was divided into three experiment trials, following a practice trial. The first trial consisted of four presentations of each load in a randomized block order. Trials two and three were performed in the same fashion with each load presented three times. Thus, subjects were exposed to 10 presentations of each load magnitude. During the experimental trial, subjects were given a cue (red light) to signal that they must estimate the next breath. The subjects made the handgrip estimate after completing the test breath.

Table 1. Asthma control subjects.

Subject	Age (yrs)	Gender/ Race*	Height (cm)	Weight (kg)	Asthma duration (yrs)	Baseline $FEV_1$$	PC20 (mg/mL)	Control Meds#
1	14.5	F/C	167	52.8	10	80	1.504	ICS, Cr
2	15.0	M/H	165	54.6	5	71	0.0683	M
3	16.2	M/C	179	79.4	5	91	0.889	ICS
4@	13.1	M/C	166	77.7	6	103	0.847	ICS, M
5	14.1	M/AA	152	66.1	1	79	5.00	ICS
6	12.2	F/AA	173	81.0	4	88	0.740	ICS, M
7	18.9	F/C	175	72.2	3	115	0.619	ICS, M

*C = Caucasian, AA = African American, H = Hispanic.
$percent predicted.
#ICS = inhaled corticosteroids; M = monteleukast; Cr = Cromolyn Sodium.
@subject asked to stop prior to reaching final stage or target drop in FEV_1 in MCH study.

Three to six control breaths separated each load presentation. Each trial was separated by a 5–10 minute break.

Methacholine challenge

A standard methacholine challenge was presented by a pediatric pulmonary clinician. Each subject then received increasing concentrations of aerosolized methacholine (0.31, 0.62, 1.25, 2.50, 5.00, 10.00 and 20.00 mg/ml). The final stage of the methacholine challenge was defined as: a) the highest dose of methacholine (20.00 mg/ml) was achieved, b) the patient requested to stop or c) a minimum drop in FEV_1 of 20% occurred.

Analysis

The handgrip MEs were averaged for each load magnitude and plotted against R load on a log-log scale. A load was considered undetected and not included in the regression analysis if the average handgrip magnitude was less than 5% on 5 or more presentations. The slope was determined by intra-individual linear regression analysis and the average slope was determined for each group. The mean V'_1 and P_{max} were averaged for each load with each group and plotted against each R load magnitude.

Comparison between groups was performed using an Analysis of Variance (ANOVA) and post-hoc between-group analysis was performed with Student-Newman Keuls method for multiple comparisons. A Chi-square test was used to determine the difference related to gender, ethnicity, age, duration of asthma, baseline FEV_1, asthma duration and PC_{20}. The significance criterion for all analyses was set at $p < 0.05$.

Results

Twelve subjects were tested, 7 asthma control and 5 ADD/ADHD+asthma. There were no significant differences between groups for height, weight, age,

Table 2. ADD/ADHD subjects.

Subject	Age (yrs)	Gender Race*	Height (cm)	Weight (kg)	Asthma Duration (yrs)	Baseline $FEV_1$$	PC_{20} (mg/ml)	Asthma Control Meds#	ADD Control meds+
1	15.9	F/C	163	90.5	6	97	>20	M	AD
2	12.8	F/C	162	79.0	12	93	1.436	ICS	MP
3	12.0	M/AA	150	66.5	11	112	9.081	ICS	MP, G
4	11.0	F/AA	161	65.9	7	70	1.587	ICS, M	none
5	14.5	M/H	163	82.7	12	83	7.109	ICS, M	none

*C = Caucasian, AA = African American, H = Hispanic
$percent predicted
#ICS = inhaled corticosteroids; M = monteleukast; Cr = Cromolyn Sodium;
+MP = Methylphenidate (Ritalin®); AD = Amphetamine and Dextroamphetamine (Aderol®); G = Gaunfacine

gender, ethnicity, baseline FEV_1 and FVC (Tables 1 and 2).

The peak inspiratory airflow was maintained for all magnitudes of resistive loads and was not significantly different between groups (Fig. 1), indicating that all subjects successfully targeted their breathing. The standard deviation of the peak airflow was greater for ADD/ADHD+asthma subjects than control asthma subjects as R increased (Fig. 2). The maximum P_{max} decreased with increasing R load magnitude (Fig. 3). The relationship between P_{max} and ΔR was not significantly different between the groups (Fig. 3).

The mean handgrip to each R load was not significantly different between groups (Fig. 4). The coefficient of variation decreased as the magnitude of the R load increased (Fig. 5). However, the coefficient of variation (Fig. 5) and standard deviation for handgrip were significantly greater ($F = 6.744$, $p < 0.001$) for the ADD/ADHD group than for the asthma control group.

The slopes of the log-log ME of the inspiratory R load for the asthma control group were less variable and greater than the ADD/ADHD+asthma group (Tables 1 and 2), but there was no group mean significant difference.

All patients' FEV_1 decreased a minimum of 20% less than baseline with methacholine challenge. The PC_{20}'s for the ADD/ADHD+asthma group were higher and more variable than those of the control subjects (Table 2).

Discussion

Children with ADD/ADHD have difficulty focusing on behavioral tasks and therefore may have increased difficulty attending to their asthma symptoms. Therefore, these ADD/ADHD+asthma patients may have greater non-compliance to their medication regimen, resulting in asthma management challenges for these unique asthma patients. To our knowledge, there is no previous study examining respiratory perception in asthma patients with ADD/ADHD.

The lack of information about respiratory symptom perception in children with co-incident asthma and ADD/ADHD may be due to few children having been identified with both conditions. ADD/ADHD has been reported in 12.1% of the asthma population [Blackman and Gurka, 2007]. Our study population base consisted of approximately 2,000 children treated for asthma by the Division of Pediatric Pulmonology at the University of Florida. While we did not sample the entire population of asthmatic children available, only 5 patients with both conditions were found within the approved recruitment period of this study. Thus, the subject

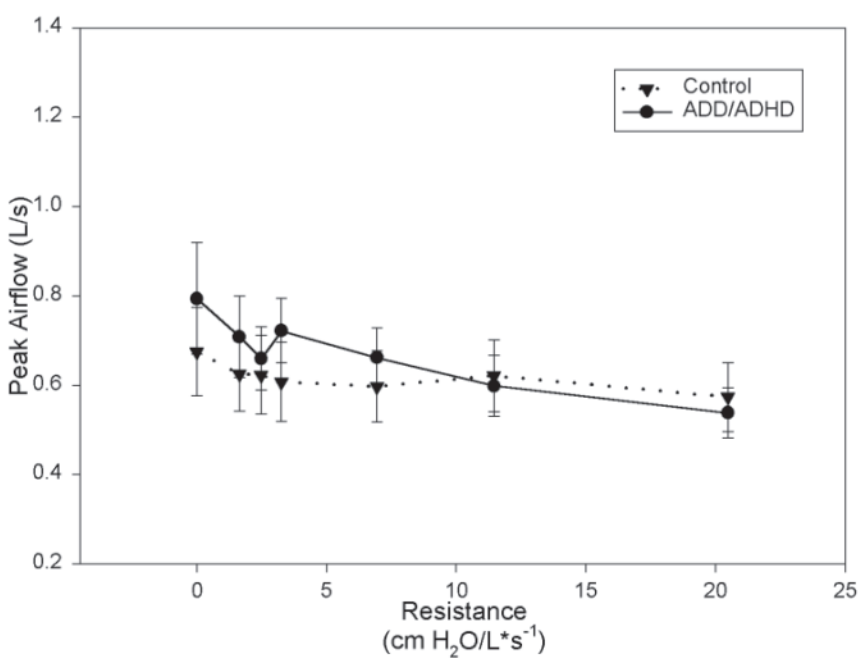

Figure 1. Peak airflow for control asthmatic subjects (dotted line) and ADD/ADHD subjects (solid line). The mean and standard deviation are plotted for each resistance magnitude. There was no significant difference in the peak flow between groups. Both groups of subjects were able to reach their target breath.

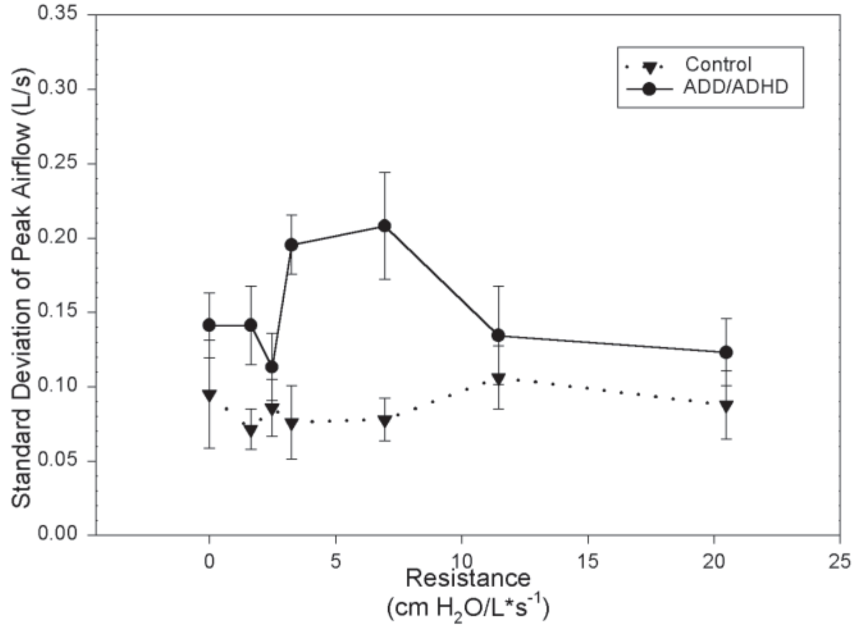

Figure 2. The average standard deviation of peak airflow for each resistive load magnitude for control asthmatic subjects (lower, dotted line) and ADD/ADHD subjects (upper, solid line).

numbers were dictated by the availability of patients with co-incident diseases (asthma+ADD/ADHD).

The two groups of children we tested were receiving medication to control their asthma. Comorbidity studies of patients with both asthma and ADD/ADHD reported that asthma and ADD/ADHD are transferred independently [Biederman et al. 1994; Blackman and Gurka, 2007]. Behavior characteristics, typical of children with ADD/ADHD include hyperactivity, impulsiveness and inattentiveness [Wilens et al. 2002; Spencer, 2002]. All our asthma patients were free from other respiratory disease, did not have an acute exacerbation within four weeks of the study, and had similar

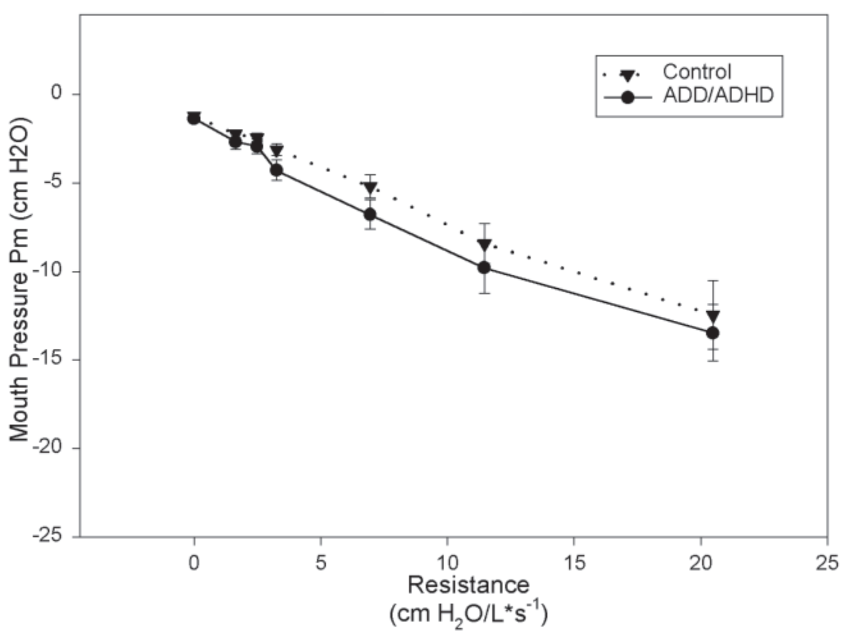

Figure 3. Peak mouth pressure (P_m) for control asthmatic subjects (dotted line) and ADD/ADHD subjects (solid line). The mean and standard deviation are plotted for each resistance magnitude. There is no significant difference between the peak mouth pressure of both groups of subjects.

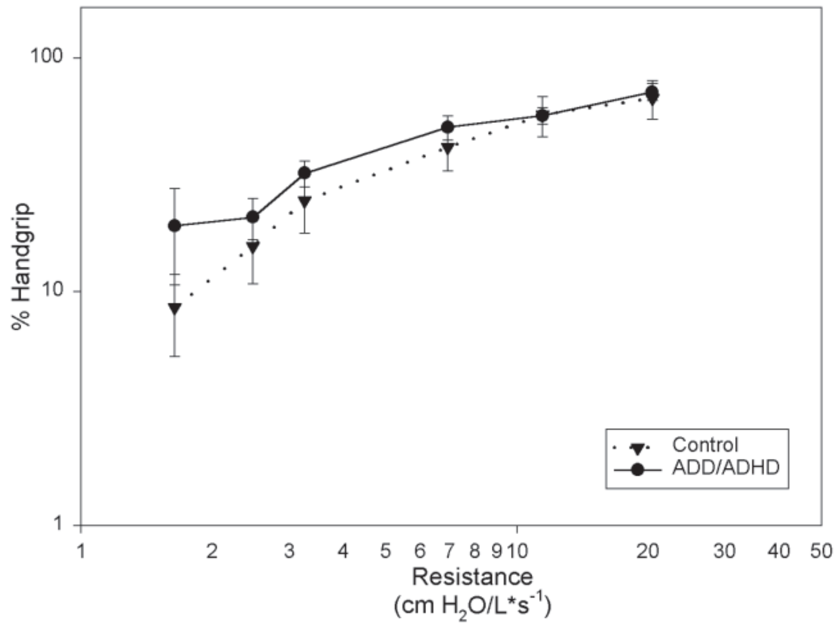

Figure 4. Relationship between group mean log percent handgrip response and log resistance for control asthmatic subjects (dotted line) and ADD/ADHD subjects (solid line). The mean and standard deviation of the % handgrip magnitude estimation is plotted for each resistance magnitude on a log-log scale. There is no significant difference between the two groups of subjects.

severity of asthma (Table 1 and 2). Therefore, the only distinguishing trait between the two groups was the diagnosis of ADD/ADHD.

However, we observed that the ADD/ ADHD+asthma children required more breaks during testing, had more difficulty remaining still during the experimental trials and had more difficulty estimating their R load perception. The ADD/ADHD+asthma group was equally able to inspire against the presented load, complete the practice trial, and voice understanding of the task. This demonstrates that they were equally capable

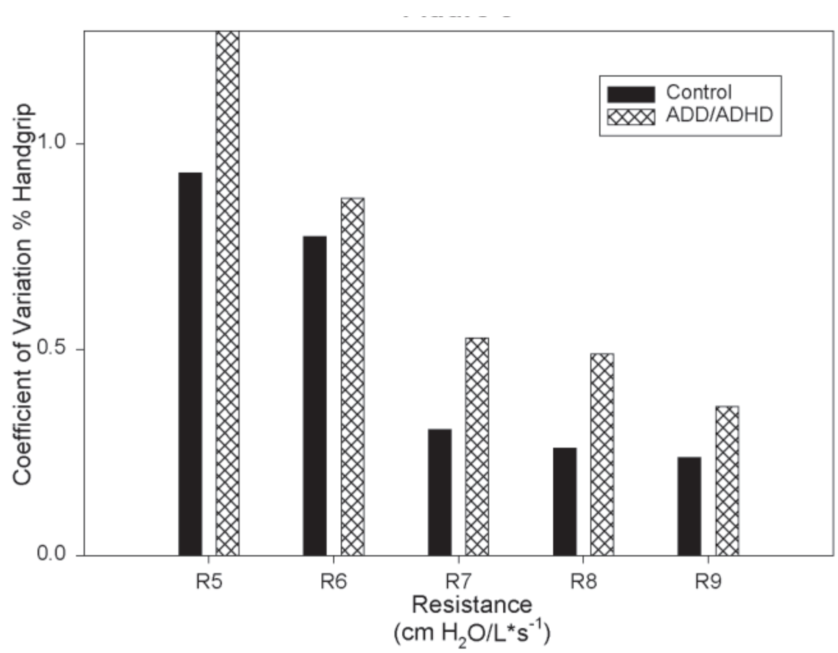

Figure 5. Coefficient of variation for the percent handgrip magnitude estimation for control asthmatic subjects (black) and ADD/ADHD subjects (checked). The ADD/ADHD subjects had significantly more variation in their responses to the respiratory loads.

of performing the task. However, the standard deviation for peak airflow was greater in the ADD/ADHD+asthma group suggesting this group had difficulty repeating the task, consistent with waxing and waning of attention. The ADD/ADHD+asthma group was equally capable of estimating the presented R load, evidenced by no significant difference in mean handgrip between groups (Fig. 4). However, the coefficient of variation for handgrip was significantly greater for the ADD/ADHD+asthma group suggesting this group had more difficulty attending to the task of estimating their respiratory sensation. Therefore, even though both groups of children were able to sense the respiratory load and give responses indicating their sensation, the ADD/ADHD+asthma group had more variation in their responses. This variation indicates reduced reliability in performing the task, suggesting an increased difficulty in attending to their respiratory status.

Subjects with ADD/ADHD have been shown to have difficulty in situations requiring sustained attention, in part due to the stimulation seeking components of the disease [Antrop et al. 2000]. In addition, these patients have been shown to have initial learning difficulties due to their inattentiveness [Douglas et al. 1990; Cahn and Marcotte, 1995], though they are able to remember a task once it has been committed to memory [Kaplan et al. 1998]. To prevent this aspect of the disease from interfering with the present experiment, we made sure the children fully understood the task. In addition, a situation with structure, order, non-distracting atmosphere, and clear expectations [Hill, 1998] was provided to minimize distractions during the experiment. Therefore, the environment in which the study took place was adapted to the special needs of these subjects.

Before each loaded breath, a light was illuminated to indicate the next breath could be loaded and the subject must estimate that breath. Borger and van der Meere [2000] reported that responses to light cues given at unpredictable, or random, intervals showed more variation in children with ADD/ADHD when compared to normal, control subjects. This variation was caused by the subjects looking away from the stimulus and neglecting to see the light cue. In the present study, the ADD/ADHD subjects may have had difficulty attending to the light cue, which would contribute to their inconsistent performance of the ME task. In addition, Cepeda et.al. [2000] reported task switching was more difficult for children with ADD/ADHD than for normal subjects. The children in the present study were asked to watch the light cue, target their breath and estimate their breath. Thus, these multiple tasks may have contributed to variability in ADD/ADHD responses.

This is important in relation to compliance with medication regimen. Behavioral studies have shown that children with ADD/ADHD have difficulty remembering tasks with organized rehearsal schedules [Douglas et al. 1990]. Taking medication for ADD/ADHD symptoms and/or asthma symptoms is an organized rehearsal schedule. This study implies that patients with both ADD/ADHD and asthma may have poor adherence to their prescribed medication regimen. In addition, children suffering from ADD/ADHD may have a disproportionate view about their level of control. Therefore, children may feel in control of their symptoms and their actions, when they are, in fact, the opposite [Gresham et al. 1998]. If a child feels in control of a situation needing medication or medical attention, that child may be more apt to be non-compliant. This problem applies to children with both ADD/ADHD and asthma since a patient may fail to use rescue medication in a potentially severe situation. Since both ADD/ADHD and asthma are chronic illnesses, it is important to address both these conditions for effective treatment.

Finally, stimulant medications [Hill, 1998] such as methylphenidate, pemoline, and amphetamine [Wilens et al. 2002,] are prescribed to alleviate some of the symptoms of ADD/ADHD such as overactive behavior and impulsiveness. In addition, methylphenidate prevents the uptake of bronchoconstrictors, such as methacholine. Therefore, the PC_{20}s of these patients may be artificially high due to their ADD/ADHD medication. The ADD/ADHD group had more variation and overall higher PC_{20}s than the control asthmatic group (Tables 1 and 2). Since methylphenidate blocks the uptake of methacholine, the results of a methacholine challenge in diagnosing these patients with asthma should be interpreted with caution.

Acknowledgements

Supported by NIH-NHLBI grant #HL47892

References

Antrop, I., Roeyers, H., Van Oost, P. and Buyesse, A. 2000. Stimulation seeking and hyperactivity in children with ADHD. *J. Child. Psychol. Psychiatry*, 41(2):225–31.

Biederman, J., Milberger, S., Faraone, S.V., Guite, J. and Warburton, R. 1994. Associations between childhood asthma and ADHD: issues of psychiatric comorbidity and familiality. *J. Am. Acad. Child. Adolesc. Psychiatry*, 33(6):842–8.

Blackman, J.A. and Gurka, M.J. 2007. Developmental and Behavioral Comorbidities of Asthma in Children. *J. Dev. Behav. Pediatr.*, 28:92–99.

Borger, N. and van der Meere, J. 2000. Visual behavior of ADHD children during attention test: an almost forgotten variable. *J. Child. Psychol. and Psychiatry*, 41(4):525–32.

Cahn, D.A. and Marcotte, A.C. 1995. Rates of forgetting in attention deficit hyperactivity disorder. *Child. Neuropsychology*, 1:158–163.

Cepeda, N., Cepeda, M. and Kramer, A. 2000. Task switching and attention deficit hyperactivity disorder. *J. Abnorm Child. Psychol.*, 28(3):213–26.

Davenport, P.W. and Kifle, Y. 2001. Inspiratory resistive load detection in children with life-threatening asthma. *Pediatr. Pulmonol.*, 32:44–8.

Douglas, V.I. and Benezra, E. 1990. Supraspan verbal memory in attention deficit disorder with hyperactivity normal and reading-disabled boys. *J. Abnorm. Child. Psychol.*, 18:617–38.

Gavin, L.A., Wamboldt, M.Z., Sorokin, N., Levy, S.Y. and Wamboldt, F.S. 1999. Treatment alliance and its association with family functioning, adherence, and medical outcome in adolescents with severe, chronic asthma. *J. Pediatr. Psychol.*, 24:355–365.

Gresham, F.M., MacMillan, D.L., Bocian, K.M., Ward, S.L. and Forness, S.R. 1998. Comorbidity of hyperactivity-impulsivity-inattention and conduct problems: risk factors in social, affective, and academic domains. *J. Abnorm. Child. Psychol.*, 26:393–406.

Hill, P. 1998. Attention deficit hyperactivity disorder. *Arch. Dis. Child.*, 79:381–4.

Julius, S.M., Davenport, K.L. and Davenport, P.W. 2002. Perception of intrinsic and extrinsic respiratory loads in children with life-threatening asthma (LTA). *Pediatr. Pulmonol.*, 34:425–33.

Kifle, Y., Seng, V. and Davenport, P.W. 1997. Magnitude estimation of inspiratory resistive loads in children with life-threatening asthma. *Am. J. Respir. Crit. Care Med.*, 156:1530–35.

Kaplan, S., Greenfield, S. and Ware, J.E. 1989. Assessing effects of physician-patient interactions on the outcomes of chronic disease. *Medical care*, 27:S110–S127.

Kaplan, S., Dewey, D., Crawford, S.G. and Fisher, G.C. 1998. Deficits in long-term memory are not characteristic of ADHD. *J. Clin. Exp. Neuropsychol.*, 20(4):518–28.

Meek, P.M. 2000. Influence of attention and judgment on perception of breathlessness in healthy individuals and patients with chronic obstructive pulmonary disease. *Nurs. Res.*, 49(1):11–9.

Spencer, T.J. 2002. Attention deficit/hyperactivity disorder. *Arch. Neurol.*, 59(2):314–16.

Wilens, T.E., Biederman, J. and Spencer, T.J. 2002. Attention deficit/hyperactivity disorder across the lifespan. *Annu. Rev. Med.*, 53(1):113–31.