

## **A Low Sodium Diet Improves Indices of Pulmonary Function In Exercise-Induced Asthma**

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### ABSTRACT

The purpose of this study was to determine if manipulation of dietary sodium could influence the severity of exercise-induced asthma (EIA). Fifteen clinically-diagnosed EIA subjects participated in a double-blind, crossover trial. Subjects entered the study on a normal salt diet (NSD), and then were placed either on a low salt diet (LSD) or high salt diet (HSD) for two weeks. Each diet was randomized with a 1-wk washout between diets before crossing over to the alternative diet. Subjects performed a treadmill test to 90% of age-predicted maximum heart rate, which was held for 5 min. Pre- and post-exercise pulmonary function tests were performed following each treatment period. 24-hr urinary sodium excretions were different ( $p < 0.05$ ) for all three diet periods (NSD = 3630 mg/day, LSD = 958 mg/day, HSD = 8133 mg/day). Contrasting pre- to post-exercise changes in pulmonary function measurements, all forced expiratory volumes and flows improved on the LSD; FVC (+0.95 liters), FEV<sub>1.0</sub> (+0.4 liters) and FEF<sub>25-75%</sub> (+0.83 liters/sec). The HSD induced reductions in FVC (-0.22 liters), FEV<sub>1.0</sub> (-0.37 liters) and FEF<sub>25-75%</sub> (-0.55 liters/sec). In conclusion, a HSD caused an increase in severity of EIA, whereas, a LSD represents a potential beneficial therapy for EIA subjects.

Keywords: asthma, airway responsiveness, dietary sodium.

## INTRODUCTION

Exercise-induced asthma (EIA) is a common condition that affects approximately 90% of asthmatics and 35-45% of those individuals with allergic rhinitis/hay fever symptoms (1). Approximately, 12-15% of the non-asthmatic general population suffers from EIA, being more prevalent in children than adults (2). EIA is clinically defined as a transient increase in post-exercise airway resistance, resulting in a greater than 10% fall in post-exercise forced expiratory volume in one second (FEV<sub>1.0</sub>) compared to pre-exercise values; and occurring within 15 minutes after strenuous exercise (at least 5-8 minutes of exercise at 85-90% predicted maximum heart rate) (3). The drop in post-exercise FEV<sub>1.0</sub> values can indicate obstruction of both the large and small airways (2).

The mechanism unique to exercise which triggers EIA in sensitive subjects is unknown. Heat and water loss associated with an increase in minute volume during exercise, along with rapid rewarming of the airways post-exercise, are believed to be causative (4). There are two popular hypotheses to explain the pathophysiology of EIA. First, airway obstruction may be caused by rapid rewarming of the cool airways following exercise, leading to vascular hyperemia, vascular engorgement and edema (4, 5). Secondly, airway dehydration resulting in hypertonicity of the airways can lead to the release of chemical mediators of inflammation, such as histamine, which then cause bronchoconstriction (5, 6).

Recent epidemiological studies have linked dietary sodium to the prevalence and severity of asthma (7-11). In general, the higher the salt intake within a population, the greater the prevalence of asthma and the greater the severity of asthma (7-9). Additionally, most (10-12) but not all (13-15), interventional studies have implicated dietary sodium and transmembrane sodium transport with the regulation of airway smooth muscle tone, and

suggests that a diet high in sodium may increase the severity of asthmatic symptoms and bronchial reactivity (10-12).

While the mechanism by which dietary sodium may lead to airway reactivity changes is not known, it is possible that dietary sodium influences smooth muscle contractility, including bronchial and vascular smooth muscle (10, 12). The influence of dietary sodium on circulating blood volume and, consequently, on hemodynamics and pulmonary function can not be ruled out as another possibility. The influence of dietary salt on EIA has not been investigated. If dietary salt enhances vascular and bronchial reactivity, then it is reasonable to expect that EIA would be worsened by elevated dietary salt and improved by dietary salt restriction. Therefore, this investigation was performed to determine if alterations in dietary sodium would influence the severity of EIA. A double-blind crossover trial was conducted to test the hypothesis that increased dietary sodium would worsen and decreased dietary sodium would improve pulmonary function variables in subjects with clinically-diagnosed EIA.

## **METHODS**

**Study Design.** The study was conducted as a double-blind randomized crossover trial over five consecutive weeks, with a one-week washout period between each two-week treatment period. All subjects entered the study on a normal salt diet (NSD, n=15), which varied according to each subject's regular dietary salt intake; after which they were randomly assigned to a low salt diet (LSD, n=7) or high salt diet (HSD, n=8) for two weeks. Thereafter, they followed a one-week washout (NSD) and then switched to the alternative diet for the remaining two weeks. A base diet was provided by means of a menu plan and required all subjects, whether on the LSD or HSD, to consume approximately 1500 mg/day of sodium.

During the HSD period, the base diet was supplemented with 10 one-gram salt capsules per day, which equaled 4000 mg/day of sodium. However, for the LSD, the base diet was supplemented with an equivalent dose of sucrose, placebo capsules. Pulmonary function tests were administered at an initial screening test and at the end of each treatment period

**Subjects.** Fifteen, clinically diagnosed, EIA subjects, comprising 9 males and 6 females, aged 18 to 36 years, participated in this study. The subjects were recruited from a university student population, and each subject gave written informed consent to participate in the study, which was approved by the Colorado State University Human Research Committee. Each subject completed a health status questionnaire prior to participating in the study. All subjects had a history of post-exercise shortness of breath, and intermittent wheezing, relieved by bronchodilator therapy after exercise. All subjects had been taking asthma medication, including short- and long-acting  $\beta_2$  agonist inhalers (14 subjects) and inhaled corticosteroids (1 subject). Subjects were told to continue to take medication that they would normally take for maintenance of their asthma (long-acting  $\beta_2$  agonist inhalers and inhaled corticosteroids). Once on the protocol, subjects were asked to refrain from using “rescue medication” (short-acting  $\beta_2$  agonist inhalers) 12-hrs prior to the exercise challenge, as these can adversely affect the pulmonary response to exercise.

An initial screening test, prior to the treatment, was used to determine which subjects were suitable for the study. Subjects refrained from using long-acting  $\beta_2$  agonists 12-hrs prior to the exercise test. The subject on corticosteroids maintained a stable dose throughout the study. All the subjects tested positive for EIA as indicated by a drop of greater than 10% in post-exercise FEV<sub>1.0</sub> values compared to pre-exercise values (16).

Blood pressure measurements, using a sphygmomanometer, were taken at the beginning of the study to screen for hypertension, and on the first day and every third day of the treatment period in order to check any abnormal rises in blood pressure. Blood pressure was also measured pre-and post-exercise. No subjects showed any abnormal rises in blood pressure at screening or during the course of the study.

**Protocol.** At the end of each treatment period, the subjects were required to perform pre-exercise pulmonary function tests. All subjects were required to have pre-exercise FEV<sub>1.0</sub> values that were at least 80% of baseline values achieved during initial screening, to ensure that the subjects' values were not depressed prior to exercise (17). An exercise test on a treadmill followed in order to induce a bronchospasm. Pulmonary function tests were then conducted 5 minutes post-exercise. A period of 5 minutes was used, as it was found that subjects become too exhausted to perform the maneuvers prior to this time frame. After all post-exercise pulmonary function tests were completed, the subjects were allowed the use of their bronchodilators 8 to 10 minutes post- exercise. Pulmonary function tests were repeated 5 minutes after bronchodilator therapy to ensure lung function had returned to near pre-exercise test values and to confirm that the decrement in flow rates was due to bronchospasm. Pulmonary function tests were conducted on each subject using a Sensormedics Vmax AutoBox D<sub>L</sub> (Sensormedics Corporation, Yorba Linda, CA) which required subjects to perform three acceptable spiograms according to the American Thoracic Society Standardization of Spirometry (18).

Each subject was instructed to avoid any strenuous physical activity 24 hours prior to the exercise test and to withhold medications, as indicated above, prior to exercise challenge. The exercise stress test protocol lasted approximately 10 minutes and required each subject to

run on a Quinton Treadmill (Model 640, Series 90, Quinton Instrument Company, WA) using a standard graded protocol of incrementally increasing workloads up to ~ 85-90% of predicted maximum heart (3). Once the target heart rate was achieved a constant load protocol was applied, which required the subject to exercise at a steady state for a further 5 minutes at the target heart rate. This protocol differed in treadmill speed and inclination for each subject in order to achieve the heart rate criteria. However, the same workload over the same period of time was performed by each subject on each study day, and speed/elevation were matched. Heart rate was determined from the ECG and monitored continuously (Quinton 4500 Stress Test Monitor, Quinton Instruments, Seattle, WA). Environmental conditions were 23°C and 50% relative humidity. During the exercise, breath-by-breath analysis of expired gases was accomplished by open circuit spirometry (SensorMedics 2900 Metabolic Cart, SensorMedics Corporation, Yorba Linda, CA). Table 2 presents the ventilatory and metabolic variables during the last minute of the 5-minute, steady state exercise test.

**Collection of 24-Hour Urine Samples.** Twenty-four hour urine excretion of electrolytes was measured at the beginning of the study and at the end of each treatment to monitor dietary sodium compliance. Each subject voided urine into 2500 ml bottles, which were collected on one of the last three days of each treatment period. The volume was recorded, and sodium and potassium concentrations were measured on a Beckman Astra analyzer (Beckman Instruments Inc., La Brea, CA) using ion specific electrodes. Urinary creatinine concentration was determined by a modified Jaffe rate reaction, using the same instrument, in order to verify the completeness of the 24-hour urine samples.

## DATA ANALYSIS

Data were analyzed using the SigmaStat v2.03 statistical package (SPSS Inc., Chicago, IL). Pre-exercise, post-exercise, delta (post- minus pre-exercise) pulmonary values and metabolic and ventilatory data were examined for the effect of diet (LSD, ND, HSD) and the presence of EIA by a repeated measures analysis of variance. A Tukey's post-hoc multiple pairwise comparison was used to isolate the differences ( $p \leq 0.05$ ). Power and sample size calculations were also computed using the SigmaStat statistical package. Power was calculated at 0.989, using a sample size,  $n = 15$ . Pulmonary function data are expressed as mean  $\pm$  SE. In addition, data were analyzed for the presence of carry-over effects between treatments, by employing an  $2 \times 2$  ANOVA cross-over design (19) on FVC, FEV<sub>1.0</sub>, FEF<sub>25-75%</sub> and PEF.

## RESULTS

All subjects completed the study and adhered to the LSD and HSD dietary protocol, and no subjects were dropped from the study due to failure to test positive for EIA at the initial screening test. Table 1 shows the means ( $\pm$ SE) for the 24-hour urinary excretion of sodium, potassium, and creatinine. The 24-hour excretion of sodium on the HSD increased by 4503 mg/day compared to the NSD ( $p < 0.001$ ), while the LSD decreased by 2672 mg/day compared to the NSD ( $p < 0.001$ ). No significant differences ( $p > 0.05$ ) were noted for potassium and creatinine excretion rates among the three different diet periods. Sodium and potassium excretions were adjusted for creatinine. Sodium excretion on the HSD adjusted for creatinine increased by 1.8-fold compared to the NSD and decreased by 1.51-fold on the LSD. No significant differences ( $p > 0.05$ ) among the three diet periods were noted for potassium excretion adjusted for creatinine.

**Table 1. 24-hour urinary excretion data.**

	<i>LSD†</i>	<i>NSD†</i>	<i>HSD†</i>
<i>Sodium (mg/d)</i>	958 ± 16.5 <sup>b</sup>	3630 ± 62.5 <sup>a</sup>	8133 ± 140.0 <sup>c</sup>
<i>Potassium (mg/d)</i>	3708 ± 63.8 <sup>a</sup>	2500 ± 43.0 <sup>a</sup>	4911 ± 84.5 <sup>a</sup>
<i>Creatinine (mg/d)</i>	1395 ± 24.0 <sup>a</sup>	1629 ± 28.0 <sup>a</sup>	1747 ± 30.1 <sup>a</sup>
<i>Sodium normalized to creatinine</i>	0.90 ± 0.02 <sup>b</sup>	2.41 ± 0.04 <sup>a</sup>	4.21 ± 0.10 <sup>c</sup>
<i>Potassium normalized to creatinine</i>	2.70 ± 0.05 <sup>a</sup>	1.46 ± 0.03 <sup>a</sup>	3.44 ± 0.06 <sup>a</sup>
<i>24-hour volume (ml)</i>	1494 ± 25.7 <sup>b</sup>	1802 ± 31.0 <sup>a</sup>	2191 ± 37.7 <sup>c</sup>

LSD = low salt diet, NSD = normal salt diet, HSD = high salt diet. † Values are means ± SE. Means with the same letter are not significantly different ( $p > 0.05$ ) among salt diets.

**Table 2. Ventilatory and metabolic variables during exercise.**

<i>INDEX</i>	<i>LSD†</i>	<i>NSD†</i>	<i>HSD†</i>
<i>V<sub>E</sub> (L x min<sup>-1</sup>)</i>	57 ± 1.4	67 ± 1.3	74 ± 1.3
<i>VO<sub>2</sub> (L x min<sup>-1</sup>)</i>	2.9 ± 0.1	2.6 ± 0.1	2.4 ± 0.1

LSD = low salt diet, NSD = normal salt diet, HSD = high salt diet. † Values are means ± SE. Significant effect of diet on all variables,  $p < 0.05$ .

Table 2 presents the ventilatory and metabolic data during the last minute of the steady state exercise. Total ventilation was greatest on the HSD and lowest on the LSD. However, VO<sub>2</sub> was lower on the HSD and higher on the LSD.

No significant differences ( $p > 0.05$ ) for each of the three trials (NSD, LSD, HSD) were observed for the pre-exercise pulmonary function tests (Table 3). All pre-exercise pulmonary function values for the three diet periods fell within the normal parameters established for males and females (20), indicating that no airflow limitations were present at rest. Pre-exercise pulmonary function indices, taken as a mean, over the three different diet periods resulted in a forced vital capacity (FVC) of 5.01 liters, forced expiratory volume in 1.0 second ( $FEV_{1.0}$ ) of 3.89 liters,  $FEV_{1.0}/FVC$  of 79.2%, and forced expiratory flow from 25-75% of FVC, ( $FEF_{25-75\%}$ ), of 3.61 liters/second.

**Table 3. Pre-exercise values for pulmonary function tests.**

<i>INDEX</i>	<i>LSD†</i>	<i>NSD†</i>	<i>HSD†</i>
<i>FVC (L)</i>	$5.12 \pm 0.28^a$	$4.94 \pm 0.29^a$	$4.97 \pm 0.29^a$
<i>FEV<sub>1</sub> (L)</i>	$3.96 \pm 0.17^a$	$3.86 \pm 0.19^a$	$3.85 \pm 0.18^a$
<i>FEV<sub>1</sub>/FVC (%)</i>	$78.73 \pm 1.86^a$	$79.20 \pm 1.84^a$	$78.73 \pm 1.93^a$
<i>FEF<sub>25-75%</sub> (L/s)</i>	$3.63 \pm 0.19^a$	$3.66 \pm 0.23^a$	$3.54 \pm 0.16^a$
<i>PEF (L/s)</i>	$8.51 \pm 0.51^{b,c}$	$7.83 \pm 0.58^a$	$8.60 \pm 0.45^b$

LSD = low salt diet, NSD = normal salt diet, HSD = high salt diet, FVC = forced vital capacity,  $FEV_1$  = forced expiratory volume in one second,  $FEV_1/FVC$  = forced expiratory volume in one second to forced vital capacity,  $FEF_{25-75\%}$  = forced expiratory flow at 25-75% of forced vital capacity, PEF = peak expiratory flow. † Values are means  $\pm$  SE. Means with the same letter are not significantly different ( $p > 0.05$ ) among salt diets.

**Table 4. Delta (Post- minus pre-exercise) values for pulmonary function tests.**

<i>INDEX</i>	<i>LSD†</i>	<i>NSD†</i>	<i>HSD†</i>
<i>FVC (L)</i>	0.95 ± 0.16 <sup>a</sup>	-0.07 ± 0.16 <sup>b</sup>	-0.22 ± 0.10 <sup>c</sup>
<i>FEV<sub>1</sub> (L)</i>	0.40 ± 0.15 <sup>b</sup>	-0.31 ± 0.13 <sup>a</sup>	-0.37 ± 0.12 <sup>a</sup>
<i>FEV<sub>1</sub>/FVC (%)</i>	3.6 ± 2.09 <sup>a</sup>	-2.13 ± 1.63 <sup>b</sup>	-4.27 ± 1.68 <sup>c</sup>
<i>FEF<sub>25-75%</sub> (L/s)</i>	0.83 ± 0.37 <sup>a</sup>	-0.33 ± 0.20 <sup>b</sup>	-0.55 ± 0.18 <sup>c</sup>
<i>PEF (L/s)</i>	-0.11 ± 0.26 <sup>a</sup>	-0.41 ± 0.32 <sup>b</sup>	-1.01 ± 0.29 <sup>c</sup>

LSD = low salt diet, NSD = normal salt diet, HSD = high salt diet, FVC = forced vital capacity, FEV<sub>1</sub> = forced expiratory volume in one second, FEV<sub>1</sub>/FVC = forced expiratory volume in one second to forced vital capacity, FEF<sub>25-75%</sub> = forced expiratory flow at 25-75% of forced vital capacity, PEF = peak expiratory flow. † Values are means ± SE. Means with the same letter are not significantly different (p > 0.05) among salt diets.

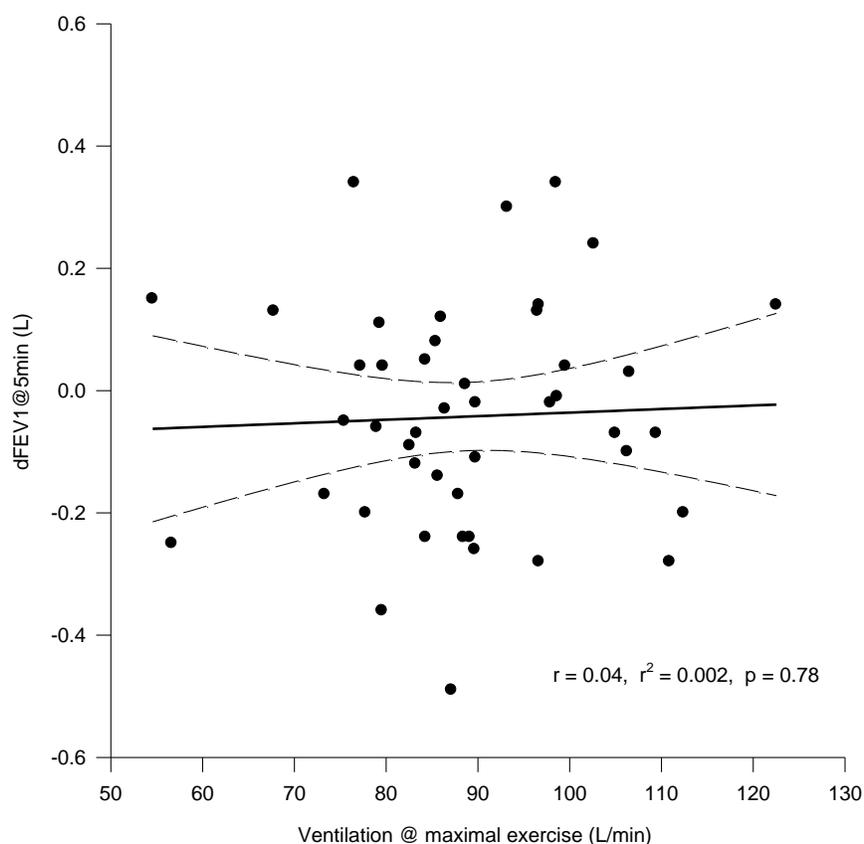
Table 4 shows the means for the delta scores (post- minus pre-exercise pulmonary function tests) for the three different diet periods. The HSD resulted in a decrease (p<0.05) in all expiratory lung volumes and flows when comparing post-exercise values to pre-exercise values, producing a decrease in FEF<sub>25-75%</sub> and PEF (peak expiratory flow) indicating both large and small airways obstruction (32). The LSD resulted in an increase (p<0.05) in post-exercise values compared to pre-exercise values in FVC, FEV<sub>1.0</sub>, FEV<sub>1.0</sub>/FVC, FEF<sub>25-75%</sub> and PEF. No significant difference was observed for FEV<sub>1.0</sub> between the NSD and HSD. An  $\eta^2$  performed on the delta scores indicated that 52% (FVC), 48% (FEV<sub>1.0</sub>), 50% (FEF<sub>25-75%</sub>) and 45% (PEF) of the variance was accounted for by the treatment. The results of the 2 x 2 ANOVA cross-over design indicated that carry-over effects were not significant (p > 0.05) for all measures of lung function. Furthermore, there were no significant period effects or group-by-period interactions.

## DISCUSSION

In the present study, subjects with EIA demonstrated decrements in post-exercise pulmonary function with elevated dietary sodium and improvements in post-exercise pulmonary function with reductions in dietary sodium. In general, there was a graded improvement in post-exercise pulmonary function as subjects changed from the HSD to the NSD to the LSD. This study represents the first report of altered post-exercise pulmonary function in EIA subjects as a result of dietary changes in salt consumption.

Dietary compliance was successful in the current study as indicated by the 24-hour urine data. The mean 24-hour urinary excretions for sodium were 8133 mg/day, 3630 mg/day and 958 mg/day for the high, normal and low salt diets respectively. Thus, a graded dose of dietary sodium was achieved in this study. Potassium excretion remained constant, as did glomerular filtration (indicated by the creatinine excretion). While the NSD was considered normal, it represented the usual dietary sodium intake for these individuals.

The ventilatory changes associated with exercise varied with diet, even though target heart rates were the same for all three conditions. Average total ventilation was greater for the HSD and lowest for the LSD, which may suggest that the ventilatory stimulus for generating post-exercise symptoms of EIA was greater for the HSD than for the LSD. However, figure 1 shows the regression of exercise ventilation against pre- to post-exercise FEV indicating that there was no relationship between ventilation achieved during exercise and the change in pulmonary function pre- to post-exercise. Therefore, effects of the differing salt diets on EIA are not the result of varying ventilatory stimuli during the exercise.



**Figure 1: Regression of maximal exercise ventilation and pre-to post-exercise changes in FEV<sub>1</sub> (dFEV<sub>1</sub>) in subjects with EIA.**

All expiratory flow rates and volumes performed pre-exercise (at rest) during the different dietary periods produced normal values (20), indicating that dietary sodium did not influence resting pulmonary function in these subjects. It is important to note that these subjects did not show evidence of intervening asthma between the periods of exercise and EIA was the only manifestation of their asthma. Post-exercise, subjects with EIA typically demonstrate decreased values in most of the variables measured during the FVC maneuver (20). EIA subjects in the post-exercise state usually have acute bronchial smooth muscle contraction, increased mucous secretion, edema of the bronchial wall and extensive infiltration of inflammatory mediators, causing obstruction of the airways (49). It is unclear whether this

obstruction is due to mucosal edema or bronchoconstriction.

In the current study, the FVC maneuver provided an indirect measure of the flow resistive properties of the lung. Pre- to post-exercise changes were evaluated. FVC was improved in a dose-response manner from HSD to LSD, suggesting less airway obstruction. The group mean fall in FEV<sub>1.0</sub> (comparing post-to pre-exercise), occurring during the initial screening test was 18% (indicating EIA). However, during both the NSD and HSD the average group mean fall in FEV<sub>1.0</sub> was 8.0% and 9.6% respectively. We did not anticipate the lack of bronchospastic responses (< 10% decrease in post-exercise FEV<sub>1.0</sub> compared to pre-exercise values on the NSD and HSD). Because the study population consisted of subjects with mild EIA, it is possible that a higher incidence of post-exercise bronchoconstriction would have been found in subjects with more severe EIA. The amount of exercise was standardized by heart rate and represented the highest target heart rate that is used clinically for this test. The total exercise duration was 8 to 10 minutes while the intensity of exercise reached high levels of VO<sub>2</sub> and V<sub>E</sub>. Therefore, neither duration nor a low intensity of exercise can account for the low incidence of post-exercise bronchospasm. During the screening test used to diagnose EIA each subject was instructed to discontinue use of baseline asthma medication; in particular long-acting  $\beta_2$  agonists were discontinued 12-hrs prior to the screening test, as it has been shown that this medication can blunt bronchoconstriction for up to 12-hrs. The one subject using the inhaled corticosteroid was receiving a stable dose and was allowed to continue using this medication during the screening test (3). In addition, the subjects were told to refrain from using the short-acting  $\beta_2$  agonists, that can serve as “rescue medication” for acute attacks. However, during the course of the study the subjects were instructed to use their baseline medication, but avoid using their “rescue medication”. The reason the subjects were allowed to

continue taking their baseline medication was a for safety. If the subjects had discontinued baseline medication during the course of the study it is conceivable that they could have experienced severe bronchospastic episodes during the exercise bout, possibly compounded further by a HSD (as three subjects experienced during a pilot study). Therefore, the residual effects of these baseline medications likely blunted the bronchoconstriction occurring during exercise and during the pulmonary function tests on all study days. This could possibly account for a group mean fall in FEV<sub>1.0</sub> on the NSD and HSD of less than 10%. Regardless of the possible protective effect of the baseline medications, a LSD improved and a HSD worsened pulmonary function in these subjects.

The authors are unaware of any previous experimental studies conducted on dietary salt intake and its influence on the post-exercise flow rates in EIA. The mechanism by which dietary sodium may influence EIA is unknown. Since the mechanism of EIA itself has not been determined, it would be speculative to suggest a possible mechanism for the interaction of sodium with EIA. Data, however, have been published on the possible relationship between asthma and dietary salt intake, and have been mainly epidemiological with limited experimental evidence. As early as 1938, Stoesser and Cook (21) reported that a LSD contributed to a decrease in symptoms in children with severe asthma. Burney (7-9) conducted epidemiological studies in England and Wales, and a strong correlation was noted between table salt purchases and asthma mortality in both men and children. Experimental studies have concentrated on the effect of manipulating dietary sodium intake on airway responsiveness. A small study demonstrated a significant increase in airway responsiveness to histamine in male and female asthmatics on a HSD (11). A randomized double-blind crossover challenge designed to test the effect on airway responsiveness to histamine in asthmatic subjects on a LSD

while taking a sodium chloride supplement or a placebo demonstrated an increase in airway responsiveness in those receiving the sodium supplementation. In addition, a significant association between bronchial reactivity and 24-hour sodium excretion was observed in males but not female asthmatics (22). A double blind, placebo-controlled crossover design study demonstrated that a change from a HSD to a LSD resulted in a significant reduction in airway responsiveness to methacholine (FEV<sub>1.0</sub>) and PEF (10). A more recent study (12) carried out an investigation to study dietary sodium intake and airway response to methacholine in relation to cellular sodium transport in asthmatics and the results suggested that a serum borne-factor found in asthmatic serum caused an increased permeability of cell membranes, thereby stimulating sodium influx into cells (which is related to the degree of hyperresponsiveness), independent of the effect of dietary sodium loading on airway responsiveness. Other studies have failed to find an association between sodium intake and asthma (or its surrogate, airways responsiveness) (13-15, ) and therefore the evidence for an association between dietary sodium and asthma remains controversial.

It is unclear how variations in dietary sodium may lead to airway reactivity changes. However, sodium transport has been implicated in many aspects of the regulation of airway smooth muscle tone (10, 12, 23). A high sodium intake has been shown to inhibit Na<sup>+</sup>/K<sup>+</sup> ATPase in erythrocytes of normotensive males (24). Enhanced dietary sodium loading expands blood volume and may trigger the release of endogenous ouabain (25, 47), that inhibits Na<sup>+</sup>/K<sup>+</sup> ATPase. The resulting inhibition of the Na<sup>+</sup>/K<sup>+</sup> ATPase would be expected to increase levels of intracellular sodium and, in turn, to increase calcium via inhibition of Na<sup>+</sup>/Ca<sup>2+</sup> exchange. Increased airway smooth muscle tone with pump inhibition is supported by animal experiments (23), but has not been shown in studies with humans. The pathological events

involved in asthma, such as the release of inflammatory mediators, microvascular leakage, and mucous secretion are also calcium dependent. Therefore, any defect in the control of intracellular calcium can account not only for increased airway responsiveness, but also increased secretory responses. The mechanisms responsible for increased bronchial reactivity may be due directly or indirectly to hormonal or chemical changes associated with increased sodium loads, or to changes in the physical properties of cell membranes.

It has been shown that airway mucosal edema can have a profound effect upon airway function (25) in EIA. An increased blood volume in the bronchial circulation caused by dietary sodium loading could exert an important influence on airway diameter. An increase in vascular volume and microvascular pressure might have substantial effects on airway function in the face of mediator-induced increased vascular permeability leading to a thickening of the mucosa (edema), thereby narrowing airway diameters; possibly amplifying the effects of increased smooth muscle tone (5).

This study has shown that a HSD leads to an increased severity of EIA and that a LSD, which improved EIA, represents a previously untried and potentially beneficial therapeutic intervention for EIA patients. These results suggest that sodium restriction used as a therapeutic intervention may be of use in EIA patients with typical and high dietary sodium intakes. Since up to 90% of asthmatic subjects have EIA, a reduction in dietary sodium may permit higher levels of exercise in this group, enabling them to receive full benefit from an exercise program.

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