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Quantifying inhaled dose of air pollutants and its effects on airway inflammation in adolescents with Asthma.

Brief Background:
Asthma is one of the most common pediatric chronic illnesses, affecting nearly 7 million children in the US and contributing to a great deal of pediatric healthcare consumption[1]. There are several risk factors that contribute to the development of asthma in addition to the severity of symptoms. Obesity, socioeconomic status and environmental exposures such as smoke and pollution among others have all been implicated[2]. Urban children in particular have higher rates of asthma[3], which some have suggested is due to exposure to increased exposure to inhaled pollutants, many of which are combustion by products from fossil fuel. Some of the most common components include NO_2, black carbon and sulfur dioxide. Many of these are components of traffic related air pollution (TRAP). Several studies have suggested a relationship between TRAP exposure and asthma exacerbations in addition to the development of new wheeze[4-6].

While physical activity has been shown to improve asthma outcomes in some studies[7], it leads to greater increases in minute ventilation (V_E), which produce in turn greater inhaled doses of air pollution[8-10]. Given this information, the effect of higher inhaled doses of air pollution on asthma need to be further elucidated.

As previously mentioned V_E is a necessary component in the calculation of inhaled dose of pollutants. In order to quantify the dose of inhaled pollutants in a large cohort of patients, it would be important to find mathematical models to calculate minute ventilation based on easily measurable variables. Equations based on HR measurements are widely used to calculate V_E. However, studies have shown that there is a great deal of variability in the relationship between V_E and HR from subject to subject. While the regression lines are often parallel to one another, the intercepts are different. This variability makes it difficult to find one model that can be used for all subjects. In an effort to reconcile this problem, Greenwald et al. developed a model in healthy adolescents where V_E was normalized by FVC and then compared to HR among other factors in a linear regression model. They developed an equation $V_E/FVC = -3.859+/- 0.101HR$ with a mean percent error of 11.3%[7]. More research needs to be done in this field to come up with new models, or validate existing models in adolescents with asthma.

Study Aims and Hypothesis:
The aims of this pilot study are two-fold. First, we aim to demonstrate a relationship between cumulative inhaled dose of pollutants and airway inflammation (Aim 1). Second, we aim to validate existing calculations for minute ventilation using HR data and FVC in our population of patients with asthma (Aim 2).

Study Design:
This pilot study will be a prospective observational cohort study of 40 adolescent subjects age 11-13 with well controlled mild-moderate asthma.

Methods:
Cardiopulmonary exercise testing (CPET): All 40 patients will undergo CPET testing on a treadmill while wearing the Polar M200 watch, which measures HR and accelerometry. Each

child will begin walking on the treadmill and gradually increase their speed with the goal of targeting 8 heart rate zones for at least 30 seconds each (>60, 60-80, 80-100, 100-120, 120-140, 140-160, 160-180, >180) During this time, the accelerometer will also categorize their activity into 5 intensities: resting, sitting, low, medium and high intensity. Minute ventilation by breath, Respiratory rate, tidal volumes and VO2 consumption will be recorded throughout the monitoring period. Spirometry will be performed before and after the testing.

To address aim 1: The 40 subjects will be monitored over a period of 48 hours. During this time, subjects will wear the Polar M200 accelerometer/HR monitor. Additionally, they will wear a pollution monitor to determine ppm of NO2 they are exposed to throughout the study period. At the conclusion of the 48 hour monitoring period, exhaled Nitrous oxide will be measured as a marker for airway inflammation.

To address aim 2: We will be modelling our analysis for this study on that performed by Greenwald et al, who demonstrated a model using HR to predict V_E/FVC: V_E/FVC = -3.859 + 0.101HR with a mean percent error of 11.3 +/- 36%. We will calculate the average minute ventilation across the 8 HR zones for each patient and plot them against V_E/FVC.

Statistical Analysis

Aim 1:

Determining inhaled dose of pollutants: From the CPET testing for each individual, we will record the average minute ventilation in each of the 8 HR zones. We will then determine how much time was spent in each of the HR zones within the 48 hour monitoring period and from this information we will know what percent of the total recorded time was spent at a given minute ventilation. Based on this data, the average minute ventilation over the 48 hour recording period can be determined. The dose of inhaled pollutants will then be calculated using the following equation:

Dose = (Concentration of inhaled pollutants x Minute Ventilation x Time)/Body Mass

We will perform linear regression models to determine the relationship between dose of inhaled pollutants and exhaled NO2. With a sample size of 40, we should be able to predict a correlation coefficient of > 0.43. Assessment of covariates will be performed as well to assess for potential confounders such as obesity, which is associated increased severity of asthma and poor fitness.

Aim 2:

We will perform general linear regression comparing the V_E/FVC and HR data obtained from the 40 subjects. We will determine the regression coefficient and p value for the equation of the best fit line. We will determine the mean percent error for our new equation.

Additionally, we will superimpose Greenwald et al's previously published equation on our data to visualize the variability between them. We will also calculate the mean percent error of their equation based on our data, which can then be compared with their published percent error recording of 11.3%.

Subject selection:

Patients will be recruited from the New York branch of the inner city asthma consortium. The subjects of this study with be patients with well controlled mild-moderate asthma age 11-13 recruited from June-September (ozone peak). Prior to initiation of the study, patients will be given ACT surveys and those whose score <19 will be excluded.

Confidentiality: Subjects will be de-identified and all patient information will be kept in locked cabinets.

Risks and benefits: This study will pose no potential risks to subjects. There will be no direct benefits to the individual patient.

Compensation and cost to subject: None with exception of transportation costs.

References:

1. Akinbami LJ, Moorman JE, Bailey C et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2012. NCHS Data Brief/ 2012;94:1-8

2. Weinmayr G, Forastiere F, Buchele G, Jaensch A, Strachan DP, Nagel G, et al. Overweight/obesity and respiratory and allergic disease in children: international study of asthma and allergies in childhood (ISAAC) phase two. PLos ONE 2014

3. Conrad L, Perzanowski M, The role of environmental controls in managing asthma in lower-income urban communities. Clin Rev Allergy Immunol. 2019 Mar 22. doi: 10.1007/s12016-019-08727-y.

4. Jung KH, Shai-I H, Beizhan Y, Moors K, Chillrud SN et al. Childhood exposure to fine particulate matter in black carbon and the development of new wheeze between ages 5 and 7 in an urban prospective cohort. Environ Int. 2012 Sept 15;45:44-5

5. McConnell R, Islam T, Shankardass K, Jerrett M, Lurmann F, Gilliland F, Gauderman J. Childhood Incident Asthma and Traffic-Related Air Pollution at Home and School. Environ Health Perspect. 2010; 118:1021. [PubMed: 20371422]

6. Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M (2017) Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ Int 100:1–31

7. Lu K, Cooper D, Haddad F, Radom-Aizik S. Four months of a school-based exercise program improved aerobic fitness and clinical outcomes in a low-ses population of normal weight and overweight/obese children with asthma. Front.Pediatr.6:380 doi:10.3389/fped.2018.00380

8. Greenwald R, Hayat MJ, Barton J, Lopukhin A. A novel method for quantifying the inhaled dose of air pollutants based on heart rate, breathing rate and forced vital capacity. PLoS ONE. 2016; 11(1):14. https://doi.org/10.1371/journal.pone.0147578 PMID: 26809066

9. Ramos CA, Reis JF, Almeida T, Alves F, Wolterbeek HT, Almeida SM. (2015) Estimating the inhaled dose of pollutants during indoor physical activity. Science of The Total Environment 527–528: 111– 118. doi: 10.1016/j.scitotenv.2015.04.120 PMID: 25958360

10. Cozza IC, Zanetta DMT, Fernandes FLA, da Rocha FMM, de Andre PA, Bueno Garcia ML. (2015) An approach to using heart rate monitoring to estimate the ventilation and

load of air pollution exposure. Science of The Total Environment 520: 160–167. doi: 10.1016/j.scitotenv.2015.03.049 PMID: 25813969