Obstruction phenotype as a predictor of asthma severity and instability in children

Ronald L. Sorkness, PhD,[a,b,c] Edward M. Zoratti, MD,[d] Meyer Kattan, MD,[e] Peter J. Gergen, MD, MPH,[f] Michael D. Evans, MS,[g] Cynthia M. Visness, PhD,[h] Michelle Gill, MD, PhD,[i] Gurjit K. Khurana Hershey, MD, PhD,[j] Carolyn M. Kercsmar, MD,[j] Andrew H. Liu, MD,[k] George T. O'Connor, MD, MS,[l] Jacqueline A. Pongracic, MD,[m] Dinesh Pillai, MD,[n] Christine A. Sorkness, PharmD,[a,b] Alkis Togias, MD,[f] Robert A. Wood, MD,[o] and William W. Busse, MD[b] *Madison, Wis, Detroit, Mich, New York, NY, Bethesda and Baltimore, Md, Chapel Hill, NC, Dallas, Tex, Cincinnati, Ohio, Aurora, Colo, Boston, Mass, Chicago, Ill, and Washington, DC*

Background: Small-airways instability resulting in premature airway closure has been recognized as a risk for asthma severity and poor control. Although spirometry has limited sensitivity for detecting small-airways dysfunction, a focus on the air-trapping component of obstruction might identify a risk factor for asthma instability.
Objective: We sought to use spirometric measurements to identify patterns of airway obstruction in children and define obstruction phenotypes that relate to asthma instability.
Methods: Prebronchodilation and postbronchodilation spirometric data were obtained from 560 children in the Asthma Phenotypes in the Inner City study. An air-trapping obstruction phenotype (A Trpg) was defined as a forced vital capacity (FVC) *z* score of less than −1.64 or an increase in FVC of 10% of predicted value or greater with bronchodilation. The airflow limitation phenotype (A Limit) had an FEV_1/FVC *z* score of less than −1.64 but not A Trpg. The no airflow limitation or air-trapping criteria (None) phenotype had neither A Trpg nor A Limit. The 3 obstruction phenotypes were assessed as predictors of number of exacerbations, asthma severity, and airway lability.
Results: Patients with the A Trpg phenotype (14% of the cohort) had more exacerbations during the 12-month study compared with those with the A Limit ($P < .03$) and None ($P < .001$) phenotypes. Patients with the A Trpg phenotype also had the highest Composite Asthma Severity Index score, the highest asthma treatment step, the greatest variability in FEV_1 over time, and the greatest sensitivity to methacholine challenge.
Conclusions: A Trpg and A Limit patterns of obstruction, as defined by using routine spirometric measurements, can identify obstruction phenotypes that are indicators of risk for asthma severity and instability. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Small-airways dysfunction, asthma exacerbation, airflow limitation, airway closure*

Variable airway obstruction is a defining characteristic of asthma, and in recent years, it has become recognized that different patterns of obstruction can have differing associations with asthma severity and instability. Gibbons et al[1] described

From [a]the University of Wisconsin-Madison School of Pharmacy, and the Departments of [b]Medicine, [c]Pediatrics, and [g]Biostatistics & Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison; [d]Henry Ford Health Systems and Wayne State University School of Medicine, Detroit; [e]the College of Physicians and Surgeons, Columbia University, New York; [f]the National Institute of Allergy and Infectious Diseases, Bethesda; [h]Rho Federal Systems Division, Chapel Hill; [i]the University of Texas Southwestern Medical Center, Dallas; [j]Cincinnati Children's Hospital; [k]Children's Hospital Colorado and University of Colorado School of Medicine, Aurora; [l]Boston University School of Medicine; [m]Ann and Robert H. Lurie Children's Hospital of Chicago; [n]Children's National Health System and the George Washington University School of Medicine and Health Sciences, Washington; and [o]Johns Hopkins School of Medicine, Baltimore.

This project has been funded in whole or in part with federal funds from the National Institute of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) and the Department of Health and Human Services (under contract nos. HHSN272200900052C and HHSN272201000052I). Additional support was provided by the National Center for Research Resources (NCRR) and the National Center for Advancing Translational Sciences (NCATS)/NIH (under grant nos. NCRR/NIH UL1TR000451, UL1RR025780, UL1TR000075 and NCATS/NIH UL1TR000154, UL1TR001082, UL1TR000077-04, UL1TR000040, UL1TR000150, UL1TR001105 and UM1AI114271). GlaxoSmithKline provided Ventolin, Flovent, Advair, and Flonase under a clinical trial agreement with the NIH/NIAID but did not have a role in the development or approval of the protocol, conduct of the trial, data analysis, manuscript preparation, or the decision to submit the manuscript for publication.

Disclosure of potential conflict of interest: R. L. Sorkness has received grants from the National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID) and the NIH/National Heart, Lung, and Blood Institute (NHLBI). E. M. Zoratti has received grants from the NIH and the NIAID and has a board membership with Wayne State University. M. Kattan has received a grant from the NIH/NIAID and is on the advisory board for Novartis Pharma. M. D. Evans, C. M. Visness, G. K. Khurana Hershey have received a grant from the NIH/NIAID. M. Gill has received a grant from the NIH/NIAID; has received a consulting fee or honorarium and travel support from the American Academy of Allergy, Asthma & Immunology; and has received payment for lectures from the American Academy of Pediatrics. C. M. Kercsmar has received a grant from the NIH/NIAID and has received personal fees from GlaxoSmithKline. A. H. Liu has received a grant from the NIH/NIAID and has received personal fees from GlaxoSmithKline and Merck Sharp & Dohme. G. T. O'Connor has received grants from the NIH and Janssen Pharmaceuticals and has consultant arrangements with AstraZeneca. J. A. Pongracic has received a grant from the NIH/NIAID; and received provision of study drugs from GlaxoSmithKline, Teva, Merck, Boehringer-Ingelheim, and Genentech/Novartis. D. Pillai has received grants from the NIH. C. A. Sorkness has received grants from the NIH/NIAID, the NIH/NNHLBI, and Novartis. R. A. Wood has received grants from the NIH, DBV, Aimmune, Astellas, and HAL-Allergy; has consultant arrangements with Stallergenes; is employed by Johns Hopkins University; and has received royalties from UpToDate. W. W. Busse has received a grant from the NIH/NIAID and has received personal fees from Boston Scientific, ICON, Novartis, GlaxoSmithKline, Genentech, Roche, Boehringer-Ingelheim, Sanofi Genzyme, AstraZeneca, Teva, 3M, PrEPBiopharm, Circassia, Regeneron, Peptinnovate, and Elsevier. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 26, 2017; revised September 12, 2017; accepted for publication September 21, 2017.

Corresponding author: Ronald L. Sorkness, PhD, University of Wisconsin-Madison School of Pharmacy, 777 Highland Ave, Madison, WI 53705. E-mail: ronald.sorkness@wisc.edu.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2017.09.047

Abbreviations used
A Limit: Airflow limitation phenotype
APIC: Asthma Phenotypes in the Inner City
A Trpg: Air-trapping obstruction phenotype
BMI: Body mass index
CASI: Composite Asthma Severity Index
CL: Confidence limit
FEF_{25-75}: Forced expiratory flow rate between 75% and 25% of forced vital capacity
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity
None: No airflow limitation or air-trapping criteria

different patterns of response to bronchial challenge, as measured by using spirometry, noting that asthmatic patients with a prominent decrease in forced vital capacity (FVC) associated with a 20% reduction in FEV_1 were more likely to have a history of frequent exacerbations. They proposed the concept that FEV_1 can be partitioned into components of airflow limitation represented as the fraction of vital capacity exhaled in the first second (FEV_1/FVC ratio) and airway closure represented as a reduction in FVC.[1] The association of premature airway closure and air-trapping with severe asthma and unstable asthma has been reinforced in multiple studies by using physiologic and imaging methods to detect air-trapping during periods of stable asthma.[2-9]

Studies from the Severe Asthma Research Program demonstrated that FEV_1 can be expressed mathematically as a hyperbolic function of its airflow limitation and air-trapping components.[5] This approach revealed that the group with severe asthma had greater air-trapping relative to the group without severe asthma and that a large bronchodilator reversal of FEV_1 was mostly due to a reversal of the air-trapping component.[5] Similarly, the Severe Asthma Research Program children with severe asthma exhibited air-trapping that was mostly reversed with bronchodilator, whereas the group with nonsevere asthma had normal lung residual volume and a bronchodilator response that was reflected only in the airflow limitation component.[6] These studies comparing groups defined by severity suggest that an assessment of airway obstruction patterns also can have value as a prospective marker of asthma instability and severity in individual persons.

The Asthma Phenotypes in the Inner City (APIC) study of the National Institute of Allergy and Infectious Diseases–sponsored Inner City Asthma Consortium evaluated a large set of variables among urban children to identify asthma clusters, factors related to difficulty in achieving asthma control, and the pathways linked to asthma severity.[10-12] In these analyses the level of airway obstruction, as defined by using FEV_1 percent predicted values, and its reversal with bronchodilation contributed significantly to the models as a risk for severe and difficult-to-control asthma.[10-12] However, the air-trapping component of obstruction was not assessed in these reports. We hypothesized that a further analysis of APIC data with regard to obstruction patterns would reveal that subjects with an air-trapping phenotype detected by using routine spirometry would exhibit the greatest asthma severity and instability.

METHODS

The APIC study has been described in detail previously.[11] Children aged 6 to 17 years with physician-diagnosed asthma were recruited from low-income census tracts in 9 urban areas. A requirement for enrollment was a history of at least 2 episodes in the past 12 months that were treated with a short-acting β-agonist. After enrollment, participants were followed for 12 months, with visits scheduled every 2 months for clinical assessments and protocol-guided adjustments of treatment based on the Expert Panel Report-3 guidelines.[13] The protocol was approved by institutional review boards from each participating center, and written informed consent was obtained from the legal guardians of participating children.

Defining obstruction phenotypes

Prebronchodilation and postbronchodilation spirometric data from the final (12-month) visit in the APIC study were used to define the obstruction phenotypes. The 2012 Global Lung Initiative reference equations[14] were used to generate predicted values and z scores for FEV_1, FVC, forced expiratory flow rate between 75% and 25% of forced vital capacity (FEF_{25-75}), and FEV_1/FVC ratio. Global Lung Initiative ethnic groupings 1 (white), 2 (black), and 5 (mixed) were assigned based on responses to the APIC demographics questionnaires. The fifth percentile of the healthy population is used conventionally as the lower limit of normal for spirometric variables, which is also a z score of -1.64. We used a z score of less than -1.64 for our definitions for consistency with commercial spirometric software reports that include either lower limit of normal or z score reference points.

Airflow limitation was defined as an FEV_1/FVC z score of less than -1.64. Air-trapping was defined as an FVC z score of less than -1.64 or a change in FVC with bronchodilation of 10% or greater of predicted value (see Fig E1 in this article's Online Repository at www.jacionline.org). These definitions were based on the concept of partitioning FEV_1 into components of airflow limitation and air-trapping[1,5] and that the air-trapping component in asthma usually improves after bronchodilation.[5,6] The cut point of a 10% predicted change in FVC was selected arbitrarily, lacking published guidelines for a minimally important change for this variable. However, a 10% change in FEV_1 with bronchodilation in children has diagnostic specificity for asthma[15] and an association with asthma instability[16] in children. Because FEV_1 changes proportionally with changes in FVC,[5] our cut point for a change in FVC should be meaningful.

Spirometry was performed on standardized equipment by trained technicians and overread centrally by certified pulmonary function technologists to ensure that the measurements conformed to American Thoracic Society guidelines.[11] Before spirometry was performed, the participants were questioned to ensure that they had not had a respiratory tract infection, a cold, or bronchitis in the preceding 4 weeks and that they had not used short-acting bronchodilators within 8 hours or long-acting bronchodilators, anticholinergic agents, leukotriene modifiers, or theophylline within 24 hours.

After baseline spirometry, bronchodilation was achieved with administration of a total of 4 actuations of an albuterol metered-dose inhaler with a valved holding chamber. If the criterion for air-trapping was met, the air-trapping obstruction phenotype (A Trpg) was assigned, and if the airflow limitation but not the air-trapping criteria were met, the airflow limitation phenotype (A Limit) phenotype was assigned. The no airflow limitation or air-trapping criteria (None) phenotype was assigned if neither air-trapping nor airflow limitation criteria were met. Children with both air-trapping and airflow limitation were included in the A Trpg phenotype to reflect the spectrum of airflow patterns associated with air-trapping and to ensure that the number of subjects with air-trapping was sufficient for meaningful statistical analyses.

Other APIC study variables

Blood samples were obtained at the initial visit of the APIC study and processed to obtain blood leukocyte counts, serum total IgE levels, and a panel of 20 allergen-specific IgE concentrations.[11] A panel of 12 common allergens was also applied as skin prick tests. Allergen sensitization was defined as a positive skin prick test response or specific IgE level of greater than 0.35 kU/L, with 22 total allergens tested.[11] Allergen sensitizations were combined further into 7 categories: roaches, pets, rodents, pollens, foods,