CHEST

Original Research

ASTHMA

Abnormal Small Airways Function in Children With Mild Asthma

Florian Singer, MD, PhD; Chiara Abbas, MD; Sophie Yammine, MD; Carmen Casaulta, MD; Urs Frey, MD, PhD; and Philipp Latzin, MD, PhD

Background: **Small airways disease is a hallmark in adults with persistent asthma, but little is known about small airways function in children with mild asthma and normal spirometry. We assessed ventilation heterogeneity, a marker of small airways function, with an easy tidal breath single-breath washout (SBW) technique in school-aged children with mild asthma and normal FEV_1 and healthy age-matched control subjects.**

Methods: **The primary outcome was the double-tracer gas phase III slope (SDTG), an index of ventilation heterogeneity in acinar airways derived from the tidal double-tracer gas SBW test. The second outcome was the nitrogen phase III slope (SN2), an index of global ventilation heterogeneity derived from the tidal nitrogen SBW test using pure oxygen. Triplicate SBW and spirometry tests were performed in healthy children (n = 35) and children with asthma (n = 31) at baseline and in children with asthma after bronchodilation.**

Results: **Acinar (SDTG) but not global (SN2) ventilation heterogeneity was significantly increased in asthma despite normal FEV_1. Of the 31 children with asthma, abnormal results were found for SDTG (≤ -2 *z* scores) in 11; forced expiratory flow, midexpiratory phase ($FEF_{25\%-75\%}$) in three; and FEV_1 in zero. After bronchodilation, SDTG, SN2, $FEF_{25\%-75\%}$, and FEV_1 significantly changed (mean [95% CI] change from baseline, 36% [15%-56%], 38% [18%-58%], 17% [9-25%], and 6% [3%-9%], respectively).**

Conclusions: **Abnormal acinar ventilation heterogeneity in one-third of the children suggests that small airways disease may be present despite rare and mild asthma symptoms and normal spirometry. The easy tidal SBW technique has considerable potential as a clinical and research outcome in children with asthma.**

CHEST 2014; 145(3):492–499

Abbreviations: $FEF_{25\%-75\%}$ = forced expiratory flow, midexpiratory phase; FENO = fraction of exhaled nitric oxide; He = helium; IGW = inert gas washout; LCI = lung clearance index; N_2 = nitrogen; SBW = single-breath washout; SDTG = double-tracer gas phase III slope; SF_6 = sulfur hexafluoride; SN2 = nitrogen phase III slope; sRaw = specific airway resistance

Small airways in the respiratory diffusion-dependent lung zone are the major site of pathology in adult patients with asthma.[1] Bronchoconstriction and airways inflammation trigger airway remodeling, which leads to patchy obstruction of small airways.[2-4] This heterogeneously impaired structure affects the function of the small airways, especially the evenness of ventilation distribution. Inert gas washout (IGW) tests, such as the single-breath washout (SBW) and multiple-breath washout tests, measure ventilation heterogeneity because spirometry is not sensitive enough.[5] Adult patients with persistent asthma have increased ventilation heterogeneity arising within peripheral preacinar (convection-dependent) and acinar (diffusion-dependent) lung zones.[6-10] Increased ventilation heterogeneity is a predictor of asthma control[7,11,12] and airway hyperresponsiveness and improves after bronchodilation[9,13] and the use of corticosteroids.[8] In children, mild asthma is the most prevalent asthma phenotype, but the degree of small airways obstruction and its reversibility is not clear in this population. In children with moderate to severe asthma, few studies have shown that ventilation heterogeneity may be elevated compared with control subjects.[14-18] Others have concluded that IGW testing is not ideal to assess bronchodilator response[19] and is too sophisticated for routine application.[20]

To overcome the latter drawback, we developed an easy dual-tracer SBW applied during normal tidal breathing. To our knowledge, the technique is the

first to be based on a validated setup according to American Thoracic Society/European Respiratory Society consensus.[21-24] The current study assessed ventilation heterogeneity in children with mild asthma and healthy control subjects to determine whether and in what proportion children with mild asthma present with functional peripheral changes. The primary aim was to compare measures of acinar and global ventilation heterogeneity between children with and without asthma. The secondary aim was to assess the effect of bronchodilation on ventilation heterogeneity and classic measures of airways obstruction in mild asthma.

Materials and Methods

Study Population

We enrolled 70 children aged 6 to 16 years from an asthma outpatient clinic and a healthy volunteer database at the Children's Hospital Bern. Children with asthma were eligible if they had a history of controlled mild asthma (daytime symptoms ≤ 2 d/wk), normal $FEV_1 \pm 1.96\ z$ scores, a prescription for low to moderate inhaled corticosteroid doses (≤ 200 μg/d fluticasone or equivalent), and no history of increased use of asthma medication during the previous 6 months.[25] Healthy children had no history of recurrent wheeze and normal FEV_1 values. Respiratory tract infection, antibiotic or oral corticosteroid use in the previous 4 weeks, and premature birth were general exclusion criteria. The study was approved by the Ethics Committee of the Canton of Bern, Switzerland (018/1). Child assent to participate was obtained, and all parents or caregivers gave written informed consent.

Study Design

The design was a prospective observational study at the Children's Hospital Bern. Children withheld their asthma medication prior to testing (short-acting β_2-receptor agonists for 8 h, inhaled corticosteroids and leukotriene receptor modifiers for 24 h). At baseline, lung function tests were done in the following order: control subjects: (1) spirometry and (2) SBW; children with asthma: (1) fraction of exhaled nitric oxide (Feno), (2) plethysmography, (3) spirometry, and (4) SBW. As repeated tests were applied, all SBW tests followed spirometry. Children with abnormal FEV_1 were excluded from the study (n = 4). Twenty minutes after inhaling 200 to 400 μg salbutamol (metered-dose inhaler; GlaxoSmithKline plc) through a spacer (Volumatic; GlaxoSmithKline plc), plethysmography, spirometry, and SBW were measured again in the children with asthma. Atopic sensitization was evaluated in children with asthma by skin prick testing of common inhalant allergens (Table 1).

Lung Function Assessments

Ventilation heterogeneity was assessed by double-tracer gas and nitrogen (N_2) tidal SBW tests.[21,22] Children breathed through an open bypass system (Exhalyzer D; Eco Medics AG).[21,23] Exhaled gas fractions were quantified by the side-stream ultrasonic flow meter (molar mass in g/mol) and an indirect N_2% sensor.[21-23] Children inhaled the double-tracer gas (or pure oxygen for the N_2 SBW) during regular tidal breathing. The double-tracer gas mixture contained 26.3% helium (He), 5% sulfur hexafluoride (SF_6), 21% oxygen, and balance N_2 from pressurized cylinders (Carbagas). The primary outcome was the slope from the tidal (alveolar) phase III from double-tracer gas and N_2 washout curves. According to the current American Thoracic Society/European Respiratory Society consensus,[24] tests were applied in triplicate to obtain the averaged slope values. The phase III slopes of each SBW test were computed by linear regression between 65% and 95% of expired volume (Fig 1[26]) and then multiplied with tidal volume.[15,24,27] The interobserver agreement for double-tracer gas phase III slope (SDTG) is strong[22] (intraclass correlation coefficient, 0.92). SDTG aggregates the phase III slopes from He and SF_6, two gases of similar convective but highly differing diffusive properties. SDTG is a specific index of ventilation heterogeneity that estimates distal (diffusion-dependent) gas mixing efficiency near the acinar lung regions.[18,22,28,29] The nitrogen phase III slope (SN2) reflects the washout behavior of a single gas only (N_2) and, thus, is an unspecific global index of ventilation heterogeneity. SN2 is influenced from inhomogeneous ventilation distribution in proximal (convection-dependent) and distal lung regions.[12,22] More details are provided in e-Appendix 1.

Feno, a biomarker of eosinophilic airway inflammation, was measured by the single-breath method with an online chemiluminescence analyzer (CLD 77 AM; Eco Medics AG). After inhaling nitric oxide-free air to total lung capacity, children exhaled against an expiratory resistance with a constant flow of 50 mL/s for at least 6 s. Feno ≥ 35 parts per billion was considered elevated.[30,31]

Table 1—*Population Characteristics*

Characteristic	Healthy Control Subjects	Children With Asthma	*P* Value
Children (boys)	35 (18)	31 (12)	.461
Age, y	11.9 ± 0.5	11.6 ± 0.6	.544
Height, cm	150.1 ± 11.9	147.9 ± 16.7	.596
Weight, kg	42.8 ± 9.9	44.0 ± 15.6	.743
Current ICS, yes (no)	0	22 (9)	…
Atopy, yes (no)	…	21 (10)	…
Feno, ppb	…	18.4 (9.0-33.2)	…
Feno ≥ 35 ppb	…	7 (23)	…

Data are presented as mean ± SD, median (interquartile range), or No. (%) unless otherwise indicated. Sex distribution was compared by Fisher exact test and anthropometric data by unpaired *t* test. ICS use was during 1 mo prior to the study. Atopy in children with asthma was determined by skin prick testing of common inhaled allergens (mixed trees, mixed grasses, cat, dog, house dust mite, and *Aspergillus fumigatus*). Children with any positive reaction were considered to be atopic sensitized. Feno = fraction of exhaled nitric oxide; ICS = inhaled corticosteroid; ppb = parts per billion.

Manuscript received April 1, 2013; revision accepted September 4, 2013.
Affiliations: From the University Children's Hospital Zurich (Dr Singer), Zurich; University Children's Hospital Bern (Drs Singer, Abbas, Yammine, Casaulta, and Latzin), Bern; and University Children's Hospital Basel (Drs Yammine, Frey, and Latzin), Basel, Switzerland.
Drs Singer and Abbas contributed equally to this work.
Funding/Support: This work was funded by the Federal Department of Economic Affairs Switzerland, Commission for Technology and Innovation, Innovation Promotion Agency [unrestricted educational grant 14435.1 PFLS-LS] and the Julia Bangerter-Rhyner Foundation.
Correspondence to: Philipp Latzin, MD, PhD, Division of Respiratory Medicine, University Children's Hospital Basel, Spitalstrasse 33, 4005 Basel, Switzerland; e-mail: philipp.latzin@ukbb.ch

DOI: 10.1378/chest.13-0784