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Clinical application of inert gas Multiple Breath Washout in children and adolescents with asthma

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Summary
Introduction: Children with asthma often have normal spirometry despite significant disease. The pathology of the small airways in asthma may be assessed using Multiple Breath Washout (MBW) and calculating the Lung Clearance Index (LCI). There are only few studies using MBW in children with asthma and existing data regarding bronchodilator effect are contradictory. The aim of the present pilot study was to compare LCI in asthma and controls and assess the effect of salbutamol in children with asthma on the LCI.
Methods: Unselected patients with a diagnosis of asthma visiting the outpatient department of our hospital between 04-2010 and 03-2011 were recruited and compared to a healthy control group. MBW was performed as inert gas MBW using sulfurhexafluorid (SF_6) as the tracer gas. Clinical data were documented and spirometry and MBW (EasyOne Pro, MBW module, NDD Switzerland) were performed before and after the use of salbutamol (200–400 μg). Healthy controls performed baseline MBW only.
Results: 32 children diagnosed with asthma (4.7–17.4 years) and 42 controls (5.3–20.8) were included in the analysis. LCI differed between patients and controls, with a mean LCI (SD) of 6.48 (0.48) and 6.21 (0.38) ($P = 0.008$). Use of salbutamol had no significant effect on LCI for the group.
Conclusion: These pilot data show that clinically stable asthma patients and controls both have a LCI in the normal range. However, in patients the LCI is significantly higher indicating that MBW may have a role in assessing small airways disease in asthma.
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Introduction

Asthma is the most common chronic respiratory disease in children and is characterised by airway inflammation and bronchial hyperresponsiveness. Most of the structural changes in asthma have, until recently, been described in the large airways. In recent years the important role of small airway disease in asthma has increasingly been appreciated. Lung tissue obtained from surgical resection, autopsy or biopsy show more extensive inflammation and airway remodelling in the peripheral airways compared to the central airways [1—3]. Even in preschool children too young to perform spirometry, airway remodelling has been demonstrated [4]. Current guidelines regarding diagnosis and management base their recommendations on symptoms and spirometry, although it is now widely accepted that spirometry is not sensitive and there is often little correlation between airway inflammation and symptoms or airway inflammation and airway obstruction measured with spirometry [5,6]. Standard spirometry provides information of obstruction in the large, central airways, but is an insensitive measure for the peripheral airways, unless gross changes are present [7,8]. There is evidence that the small airways may be reflected in Multiple Breath Washout (MBW) and the Lung Clearance Index (LCI). In Cystic Fibrosis (CF), LCI has a higher sensitivity than spirometry for measuring extent and progression of lung disease [9,10]. In asthma, changes of the LCI are likely to be more subtle. Existing data found that the LCI is significantly elevated compared to healthy controls, but is still within the normal range. It can therefore not be used to diagnose asthma on an individual level [10—12]. Results regarding bronchodilator response on LCI in paediatric asthma patients are contradictory. In younger patients a significant effect on FEV_1 was seen, without a change in LCI. One study with older children showed no improvement of LCI, whereas Gustafsson et al. showed a small improvement of LCI after the administration of salbutamol [10,12—14].

The primary objective of this pilot study was to assess the LCI and the effect of salbutamol on LCI in paediatric asthma patients. We hypothesized that the LCI is more sensitive to assess small airways changes in children with asthma than spirometry. Secondary aims were to compare the LCI of paediatric asthma patients to healthy controls, and to assess the association between standard spirometry (FEV_1) and LCI.

Methods

Study design

This is a prospective, cross-sectional observational pilot study in an unselected group of children and adolescents with asthma compared to a healthy control group, where MBW was measured in both, patients and controls. In patients, spirometry and MBW were compared pre- and post inhalation of salbutamol.

Setting and participants

Measurements were performed at the Department of Paediatrics of the Marien Hospital Wesel between April 2010 and March 2011.

Patients were recruited from the asthma outpatient department and were eligible if they had a confirmed diagnosis of asthma and a minimum age of four years. Exclusion criteria were presence of other severe or chronic lung diseases, exacerbations in the last 6 weeks or changes in asthma medication over the last 6 weeks. Outpatients in a stable clinical state were recruited prior to their following routine visit to the department. The study was then incorporated into the routine diagnostic workup for those patients who agreed to participate.

MBW measurements previously derived from healthy children and adolescents using the same protocol, equipment and software for analysis were used as the reference data set [15,16]. Definition of a healthy individual excluded diagnosis of asthma, presence of other severe or chronic (lung) diseases, prematurity and presence of other severe diseases.

The study was approved by the ethics committee of the Medizinische Hochschule Hannover. Informed written parental consent and if applicable children's assent were obtained prior to the measurements.

Protocol

All asthma patients aimed to perform a set of 2—3 technically acceptable MBW measurements plus subsequent spirometry. Measurements were performed pre and post 200—400 μg of inhaled salbutamol. Post-bronchodilator lung function testing started after an interval of 10—15 min according to the ATS/ERS standard [17]. Healthy controls only performed a baseline MBW.

Demographic data were obtained and documented prior to the measurements. Additional clinical information regarding severity of asthma and degree of asthma control according to the GINA guidelines, current medical treatment and results of the Asthma Control Test (ACT) were obtained from outpatient records [5].

For children between 4 and 11 years of age the childhood ACT was used. Children older than 12 years of age received the adult ACT.

MBW

MBW measurements were performed using the EasyOne Pro, MBW Module (NDD Medical Technologies, Zurich, Switzerland). The ultrasonic technology was described elsewhere [18].

Briefly, the system consists of a side stream ultrasonic transducer for temperature and humidity independent sampling of the molar mass (MMss), a mainstream ultrasonic transducer for flow sampling and a side stream infrared CO_2 analyser (DUET ETCO2 Module, Welch Allyn OEM Technologies, Beaverton) to correct the MMss signal for exhaled CO_2. The gas bias flow system provides valve-controlled tracer

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