Phase-contrast MRI for Detection of Mild Systemic Hemodynamic Response after Segmental Allergen Challenge in Asthmatic Patients

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Rationale and Objectives: Detection of a systemic hemodynamic response in patients suffering from allergic asthma after segmental endobronchial allergen challenge using phase-contrast magnetic resonance imaging (MRI).

Materials and Methods: Nine asthma patients and four healthy volunteers were examined using MRI (1.5T) before (0 hour), 6 hours, and 24 hours after segmental allergen challenge. Two-dimensional phase-contrast MRI measurements were performed in the aorta (AO) and in the pulmonary artery (PA). In addition, short-axis balanced steady state free precession cardiac cine MRI was performed. Maximum systolic flow, maximum flow acceleration, acceleration volume, acceleration time, distensibility, ejection fraction, stroke volume, end-systolic/diastolic volume, cardiac mass, heart rate (HR), and cardiac output (CO) were determined. Spirometry and bronchoalveolar lavage were also performed.

Results: In patients with asthma, maximal systolic flow and maximal flow acceleration increased 6 hours after provocation in the AO (112.3% and 118.9%, respectively) and PA (113.9% and 116.0%, respectively) compared to baseline (100%, $P < .05$). HR and CO increased significantly at 6 hours (115% and 118%, respectively) compared to baseline (100%, $P = .003$). In healthy subjects, almost all MRI-derived hemodynamic parameters did not significantly change at 6 hours and were significantly lower than baseline values at 24 hours ($P < .02$). Twenty-four hours after allergen challenge, all MRI-derived flow parameters were significantly lower in the control group compared to the asthma group ($P < .05$). HR, CO, and cardiac function parameters measured at 24 hours showed no significant difference comparing the two groups ($P > .05$).

Conclusions: In asthmatic patients, MRI-derived hemodynamic parameters using phase-contrast MRI are slightly altered after segmental allergen provocation compared to normal controls indicating a mild systemic reaction to local allergen challenge.

Key Words: Phase-contrast MRI; asthma bronchiale; endobronchial allergen challenge.

Asthma is a serious health hazard affecting 300 million people worldwide with an annual death rate of 250,000 patients (1,2). Allergic asthma is a chronic inflammatory disease of the airways caused by an inappropriate immune response to allergen exposure (3,4). To date, the pathophysiological mechanism is still incompletely understood.

Segmental allergen challenge is a widely accepted and powerful tool to study mechanisms of airway inflammation and to test the efficacy of anti-inflammatory compounds in early clinical trials (5). One standard parameter to assess the severity of inflammation and the response to anti-inflammatory drugs is the concentration of eosinophils in the bronchoalveolar lavage (BAL) fluid. Determination of the eosinophilic cell count requires repeated bronchoscopies (6) for induction and read out of the inflammatory response that adds complexity and invasiveness especially to volunteers. Usually segmental allergen challenge involves one to four segments of the lung resulting in a local inflammatory response strictly limited to the challenged segments without any reported relevant systemic hemodynamic side effects (7–9). Although both provocation and response after segmental

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allergen challenge are local, there might be nevertheless a mild systemic hemodynamic response.

Magnetic resonance imaging (MRI) has evolved into an effective tool for noninvasive assessment of cardiopulmonary anatomy and function (10–15). Phase-contrast MRI (PC-MRI) is a well-established technique for quantification of pulmonary and systemic hemodynamics (16,17). Therefore the purpose of this study was to investigate if a systemic hemodynamic response in asthmatic patients after local allergen challenge is present using high temporal resolution PC-MRI compared to normal controls.

MATERIAL AND METHODS

Patient Population

Nine asthmatic patients (seven men and two women; age 40.5 ± 7.8; range 27–49 years) and four healthy volunteers (four men; age 43.8 ± 6.2 years; range 36–50 years) without significant age difference ($P = .44$) participated in this MRI study. All subjects were nonsmokers and did not suffer from an acute bronchitis up to 4 weeks before the study. The body mass index of the asthmatic patients was 24.0 ± 2.7 kg/m^2 and of the healthy volunteers was 24.8 ± 3.1 kg/m^2 ($P = .76$). Local ethics committee approval was obtained and all volunteers gave written informed consent. Volunteers with contraindications to MRI (ie, implanted pacemakers, metallic foreign bodies in the orbits or claustrophobia) were excluded.

Segmental Allergen Challenge and BAL

The nine participating patients had mild intermittent allergic asthma as defined in the Global Initiative for Asthma (GINA) guidelines (3) with positive response to inhaled allergen (either grass mix or house dust mite). Each patient had a positive skin prick test to one or more of the common allergens (mixed grass pollen, mixed tree pollen, rye pollen, mugwort pollen, ribwort pollen, *Dermatophagoides pteronyssinus*, *D. farinae*, cat fur, dog hair, mixed feather, *Alternaria*, *Cladosporia* from Abello [Bornheim, Germany] or ALK-Scherax [Hamburg, Germany]) (18). Bronchial responsiveness to metacholine was determined but not regarded as an inclusion criterion (5,18).

The four healthy controls had no history of allergic reactions, a negative skin prick test, normal lung function determined by spirometry, and no bronchial responsiveness to metacholine.

All subjects underwent standardized bronchoscopies with segmental allergen challenge and BAL as described previously (5–8). After baseline BAL in the left lower lobe, four segments were instilled in case of asthmatic patients with 10 mL of normal saline (S: one segment in the middle lobe unaffected by allergen) to control for specificity of the procedure, low dose of allergen (LA: one segment of the right upper lobe) equivalent to one-tenth of standard dose, or a standard dose of allergen in two segments of contralateral lungs (SA: right middle lobe and left lingula) to study intraindividual reproducibility (5,18). The healthy volunteers had three instillations receiving only one standard dose of allergen because reproducibility was not a question. One additional segment in the right middle lobe was lavaged with 150 mL of saline at the first bronchoscopy to increase the total number of recovered cells for separate in vitro experimentation. Twenty-four hours after the first bronchoscopy (the time of maximum eosinophilic inflammation), all subjects underwent a second bronchoscopy under the same standardized conditions, and all challenged segments were lavaged to assess cellular response at 24 hours (5,18). In all participants, two bronchoscopies were performed. The general principle of the bronchoscopic procedure with sample preparation has been described in detail (5). The number of eosinophils in BAL fluid was determined.

Spirometry

In addition to the BAL cell count, as an indicator of the allergic reaction, spirometric measurements were performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) at the time of the MRI scans at 0, 6, and 24 hours and served as additional noninvasive parameter to determine impaired lung function due to allergen challenge (19). The following spirometric values were determined: forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1 predicted, and FEV_1/FVC ratio.

MRI Protocol

All examinations were performed on a commercially available 1.5T magnetic resonance (MR) system (Avanto; Siemens Medical Systems, Erlangen, Germany) equipped with the manufacturers eight-channel torso phased array coil (Siemens Medical Systems). MRI scans were acquired before (0 hour), 6 hours, and 24 hours after segmental allergen challenge.

To assess the systemic hemodynamic effect of local segmental allergen challenge, phase-contrast flow measurements were performed in the ascending aorta (AO) and the main pulmonary artery (PA) using a through plane retrospectively electrocardiographically (ECG)-gated spoiled gradient echo sequence (FLASH) during free breathing. MRI was performed during normal free breathing because inspiratory or expiratory breath holds change the intrathoracic pressure, thus the pulmonary vascular resistance, and might alter hemodynamic parameters (20,21). The following acquisition parameters were used: echo time (TE)/repetition time (TR) = 2 ms/20 ms, flip angle = 30°, slice thickness = 5 mm, field of view = 345 × 460 mm^2, matrix size = 192 × 256, number of averages = 3, in-plane resolution = 1.8 × 1.8 mm^2, bandwidth/pixel = 930 Hz/pixel, 75 reconstructed phases, and velocity encoding gradient = 150 cm/s. In addition, retrospectively ECG-gated cine balanced steady state free precession (bSSFP) sequences were acquired during short