Pulmonary gas exchange response following allergen challenge in patients with allergic asthma

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ABSTRACT: Pulmonary gas exchange was studied in 8 patients with allergic asthma before and after allergen challenge. Ventilation-perfusion relationships were assessed by the multiple inert gas elimination technique and forced expiratory flow by conventional spirometry. Measurements were made before, 7–8 minutes, and 0.5, 2.5 and 5 hours after challenge.

During baseline conditions all patients showed normal forced expiratory flow (FEV₁; 3.9±0.77 l) and gas exchange expressed as the dispersion of pulmonary blood flow, log SDQ (0.35±0.08), (one of the common descriptors of ventilation-perfusion (V/Q) inequality). Immediately after challenge there were significant decreases in FEV₁ (to 2.3±0.75 l) and arterial P0₂ (from 13.1±0.9 to 9.5±1.2 kPa). The developed ventilation-perfusion inequalities were similar to those found in other asthma studies, i.e. mainly a broad (log SDQ increased to 0.73±0.30) and sometimes bimodal distribution of the perfusion. Thirty minutes after challenge FEV₁, significantly improved to 3.2±1.18 l while log SDQ remained high (0.71±0.32). Two and a half hours after challenge log SDQ was reduced and almost normalized to 0.38±0.07. Five patients developed a late phase reaction with decreasing flow rates after 5 hours. Three of these patients also showed increased log SDQ. There was no clear relationship between gas exchange mismatch and reduced forced expiratory flow.

The results support the hypothesis that reduced expiratory flow and gas exchange impairment are caused by different pathophysiological mechanisms. Eur Respir J., 1992, 5, 1176–1183.

Several studies have examined gas exchange impairment in nonallergic (intrinsic) asthma with the multiple inert gas elimination technique. Abnormally broad and sometimes bimodal distributions of the perfusion on different ventilation-perfusion ratios have been shown in patients with asymptomatic asthma [1] as well as in patients with clinical signs of asthma [2] and in asthmatics after methacholine challenge [3]. Data from these studies suggest that spirometric and gas exchange abnormalities in asthma are caused by different pathophysiological events: the gas exchange mismatch might be induced by secretion and oedema in the small airways [4]. Thus, several studies have been accomplished in patients with nonallergic asthma but the only reported study (abstract) in allergic (extrinsic) asthma considers acute phase only [5].

The aim of the present study was to examine the nature of the gas exchange disturbance and its relation to forced expiratory flow after bronchial challenge with allergen in patients with allergic asthma. The time course of gas exchange impairment and reduced forced expiratory flow were compared during a 5-hour period to include a possible late phase reaction. Young, otherwise healthy patients with normal spirometric data were studied during an asymptomatic phase.

Patients and Methods

Patients

Eight patients (6 males) with allergic asthma (mean age 26 yrs range, 17–38) participated in the study. All patients were free from medication. Patient data are shown in table 1. All patients had a positive skin prick test and a PC₂₀ FEV₁, for the allergen (i.e., the interpolated concentration of allergen yielding a decrease in FEV₁ of ≥20% of the value obtained after inhalation of the diluent) of <10,000 BU (Biologic Units, Spectralgen, Pharmacia, Uppsala, Sweden), as assessed in pretial tests. Prior to the start of the study, all patients performed baseline routine forced spirometry, results being within the normal range [6].
Routine pulmonary X-ray before the study was normal in all subjects. All patients were studied in autumn and winter to avoid the pollen season. Informed consent was obtained in each case, and the study was approved by the human ethics committee at Huddinge hospital.

**Bronchial challenge**

After baseline lung function measurements, the bronchial provocation started with inhalation of a nebulized solution of the diluent followed by inhalation of allergen in increasing doses, each increment representing a tenfold increase of the former concentration. The allergen challenges were performed with an Aiolos System Inhaler (Karlstads syrgasfabrik, Karlstad, Sweden) which are designed to generate an aerosol in which 80% of the mass represent particles <3.75 μm, one ml of each concentration was inhaled. Spirometry was measured 15 min after starting the inhalation. The allergen provocation started at 1 or 10 BU (determined from the pretrial challenge). The provocation was stopped when FEV1 had decreased to ≤80% of the post-diluent value. The patients were continuously supervised by a physician with necessary equipment and drugs to prevent any severe asthma attack. No patient needed treatment during the study despite different degree of breathlessness. However, 3 patients were given bronchodilators and corticosteroids before leaving the department (after the investigation) to completely reverse any bronchoconstriction.

The lung function measurements were repeated immediately after (7-8 minutes) and at 0.5, 2.5 and 5 hours following the bronchial challenge.

**Symptoms**

At the time of the ventilation-perfusion (VA/Q) study, the patients were questioned concerning symptoms. Breathlessness was scored according to an assumed linear scale constructed by BORG [7], ranging from 0 (none) to 10 (extremely severe).

The interview was carried out by the same investigator on all occasions. Blood pressure, measured noninvasively, and heart rate, by palpation were recorded. Respiratory rate was recorded by inspection and auscultation.

**Spirometry**

Forced expired vital capacity (FVC), forced expired volume in 1 second (FEV1), and forced expiratory flow at 25% of FVC (MEF25) were measured by means of a low resistive bellows spirometer (Collins, USA). The best FEV1 value of 3 measurements was accepted. MEF25 was read off manually from the flow-volume curve of the measurement with the best FEV1. All patients were coached by the same technician and were familiar with spirometric measurements.

**Ventilation-perfusion relationships**

The distributions of VA/Q ratios were assessed by the multiple inert gas elimination technique [8, 9]. This method requires measured or estimated values of arterial, pulmonary arterial and mixed expired concentrations of inert gases during constant infusion of the inert gases. A modified technique was used with measured values for arterial blood and mixed expired gas and assumed values for cardiac output and mixed venous inert gas concentrations [8]. The assumed value for cardiac output was calculated from the measured oxygen uptake and an estimated arterial-mixed venous oxygen content difference of 5 ml-100 ml blood. Theoretical work has shown that the VA/Q dispersion indices are very insensitive to the estimate of cardiac output [10].

For the gas exchange study 2 short catheters were inserted, one into the brachial artery and the other into a peripheral vein of the other arm. Intravenous infusion of inert gases, (SF6, ethane, cyclopropane, enflurane, ether and acetone) dissolved in saline, was started and maintained for 60 minutes before measurements. Infusion rate was 3 ml·min⁻¹. The patient was comfortably seated. At the time of
measurements 5 ml arterial blood and 30 ml mixed expired gas samples were taken in duplicate when ventilation and expired O\(_2\) and CO\(_2\) levels, measured breath by breath on a mass-spectrometer (Centronic, MGA200, Croydon, England), were stable. Each patient wore a nose-clip and all expired gas passed through a heated metal mixing chamber. Minute ventilation was measured using a vortex flowmeter (Bourns LS 75 ventilation monitor) and oxygen uptake was calculated. The samples were analysed for inert gas concentrations by a gas-chromatograph (Sigma 3, Perkin-Elmer, Norwalk, Connecticut, USA). Retention and excretion ratios were computed and the solubility of each inert gas was determined by a two step procedure. Finally the VA/Q distribution was estimated [8]. Of the duplicate runs, the VA/Q distribution that had the best fit to retention/excretion data (lowest remaining sum of squares, RSS) was used for statistical analysis.

From the VA/Q distributions, data were derived for shunt (perfusion of lung regions with VA/Q ratios <0.005); "low VA/Q" (perfusion of lung regions with 0.005 <VA/Q ratios <0.1); "high VA/Q" (ventilation of lung regions with 10 <VA/Q ratios <100), and dead space (ventilation of lung regions with VA/Q ratios >100). The dispersion of the perfusion and ventilation on different VA/Q ratios are expressed as the logarithmic standard deviations of the perfusion distribution (log SDQ) and ventilation distribution (log SDV). Log SDQ and log SDV are thereby expressing the degree of overall ventilation-perfusion mismatch. Qmean and Vmean show the mean VA/Q ratios of the perfusion and ventilation distribution, respectively.

Blood gas analysis

2 ml arterial blood was drawn for determination of oxygen and carbon dioxide tensions (P\(_{AO2}\), P\(_{ACO2}\)) and pH. Standard electrode techniques (ABL2, Radiometer, Copenhagen, Denmark) were used. Alveolar oxygen tension (P\(_{AO2}\)) for the calculation of alveolar-arterial oxygen tension difference (A-aPo\(_2\)) was estimated from a simplified formula:

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P_{AO2} = P_{O2} - \frac{P_{ACO2}}{0.8}
\]

where P\(_{O2}\) is inspired oxygen tension, and 0.8 is an assumed gas exchange ratio (R). The CO\(_2\) production was not measured, thus R-value is assumed.

Statistics:

All data are presented as mean and standard deviation. Comparisons were performed by analysis of variance (ANOVA) with Fisher's Protected LSD test. A p-value <0.05 was considered significant. Relationships between spirometric and gas exchange variables were investigated with linear regression analysis.

Results

The multiple inert gas elimination technique

The fit of the derived VA/Q distributions to the measured retention and excretion data, expressed as the remaining sum of squares (RSS), did not exceed 6.0 in more than 7 of all 40 measurements. This is in good accordance with the requirements as defined by Wagner and West [11].

Before challenge

Mean values and dispersions (standard deviations) from the measurements before challenge as well as after challenge are shown in table 2. The distribution curves of ventilation and perfusion on different VA/Q ratios before and after challenge in 4 patients are shown in fig. 1. Before challenge with allergen all patients showed a narrow unimodal distribution of the ventilation and perfusion with a dispersion of the perfusion on a logarithmic scale (log SDQ) ranging between 0.23 and 0.50 and averaging 0.35, which should be compared with the upper 95% confidence interval of 0.6 [2], (table 2 and fig. 1, left panels). No significant shunt and no perfusion to areas with low VA/Q were shown. Nor was there any ventilation to areas with high VA/Q in any patient. Dead space ventilation averaged 30% of the total ventilation. Arterial P\(_{O2}\) and P\(_{ACO2}\) were within the normal range, as well as pH. Likewise mean A-aPo\(_2\) was normal (0.45 kPa). Forced expiratory volume and flow measured as FEV\(_1\) and MEF\(_{25}\) were also within the normal range [6]. Heart and respiratory rate, systemic blood pressure, minute ventilation and O\(_2\) uptake were normal. All but 2 patients were symptom-free with no breathlessness (0 according to the "Borg scale"). One patient scored 0.5 (extremely weak) and the other 1.0 (very weak) for breathlessness.

After challenge

Immediately (7-8 minutes) after the bronchial challenge, there was a clear widening of the distribution curve of the perfusion in all patients and log SDQ increased significantly to a mean of 0.73 (table 2 and fig. 1, second panels from the left). Qmean was moved towards lower VA/Q ratios and Vmean was similarly moved towards higher VA/Q ratios. In 2 patients a bimodal VA/Q distribution of the perfusion appeared with the additional VA/Q mode within low VA/Q regions. (Patient no 5: 1%, patient no 8: 23% of cardiac output; fig 1). Minimal shunt was seen in two patients (0.3 and 0.1%, respectively). Dead space ventilation was slightly but significantly increased to 37%. Mean P\(_{AO2}\) was significantly decreased (from 13.1 kPa to 9.5 kPa) whilst P\(_{ACO2}\) (from 5.4 to 5.3 kPa) and pH (7.40) were unchanged. Mean A-aPo\(_2\) was significantly increased to 3.8 kPa.
Forced expiratory volumes and flows were significantly lower immediately after challenge with a mean FEV₁ of 2.26 l and a mean MEF₂₅ of 0.39 l·s⁻¹. All patients became breathless with a score ranging from 3 (moderate) to 5 (strong) (mean 3.9) according to the Borg scale. No changes were shown in ventilation, breathing, and heart rates, blood pressure or oxygen uptake (table 2).

30 minutes after the challenge there was a significant increase in forced expiratory volume (FEV₁) towards baseline conditions (mean 3.18 l). The ventilation-perfusion mismatch measured as log SDQ (mean 0.71) was, however, unchanged compared to immediately after challenge. Perfusion to regions with low VA/Q was seen in patients no. 6 and 8 (5 and 14%, respectively), and one of
Fig. 1. Ventilation-perfusion distributions in patients nos. 1, 3, 5 and 8 before and during a 5 h period after allergen challenge. The perfusion distribution curve is shown with closed circles and the ventilation distribution curve with open circles. The patients show a considerable heterogeneity in the patterns of response after challenge. Patient no. 1 developed a broader perfusion distribution (higher log SDQ) after 5 h compared to immediately after challenge, despite a lower FEV1 immediately upon challenge. Patient no. 3 had a low FEV1 and an increased log SDQ upon challenge. After 5 h, FEV1 was reduced again to the same level together with a normal log SDQ. Patient no. 5 showed a moderate reaction immediately after challenge but after 5 h this patient developed low FEV1 and a ventilation-perfusion impairment with a bimodal distribution. Patient no. 8 reached a low FEV1 and had an increased log SDQ with a typical bimodality of the perfusion distribution immediately after challenge. No late phase reactions was seen in this patient.
these had shown a low $V_{A/Q}$ mode immediately upon the challenge (fig. 1, patient no. 8). No significant shunt was shown. Breathlessness was less marked than immediately after challenge in six patients, unchanged in one patient and absent in one.

2.5 hours after challenge the forced expiratory flow was further increased and nearly reached the baseline values. The $V_{A/Q}$ distributions were significantly improved with a log SDQ no longer different from the baseline value. Only 2 patients complained of breathlessness, and both scored it as weak. Ventilation and oxygen uptake became significantly higher after 2.5 hours.

Five hours after challenge expiratory flow rates had again decreased in 5 patients with mean reductions (for the whole group) in $FEV_1$ of 0.53 l and $MEF_{25}$ of 0.11 l/s compared to the 2.5 h values. Three of these patients also showed clearly increased log SDQ. However, the change of log SDQ was not significant for the group as a whole. Two of the patients, nos. 1 and 5, also had regions with low $V_{A/Q}$ ratios of 1.3 and 5% of perfusion, respectively. One patient had a shunt of about 3%, the other less than 1%. All 5 patients with decreasing $FEV_1$ complained of breathlessness scored from 2 (weak) to 7 (very strong).

Mean score of all patients was 1.9 which was significantly higher than baseline. Of the 3 patients without decreasing forced expiratory flow 5 hours after challenge none showed increased log SDQ, shunt, low $V_{A/Q}$ mode, or suffered from breathlessness. Ventilation and oxygen uptake were significantly higher also after 5 hours.

**Relationships between spirometry and gas exchange**

The decrease in $FEV_1$ after challenge was accompanied by an increase in log SDQ in all patients. When looking at individual patients, there was a slight but significant ($p<0.05$) correlation between log SDQ and $FEV_1$ over time in 5 of the patients. However, the slope coefficient varied considerably between the patients, from -0.05 to -0.67, precluding the calculation of log SDQ from $FEV_1$ or vice-versa. No correlation could be demonstrated between $FEV_1$ and log SDQ for the patient group at any time after challenge (fig. 2), the correlation coefficients varying from -0.5 to 0.3. Thus the relation varied from a small change in log SDQ despite a large decrease in $FEV_1$ in one patient to a large increase in log SDQ despite a small decrease in $FEV_1$. No significant correlations were found. One symbol for each subject. BC: before challenge; 0: immediately after challenge; 0.5: 0.5 h after challenge; 2.5: 2.5 h after challenge; 5 h after challenge.

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**Fig. 2.** - Regression analysis of log SDQ on $FEV_1$ (% predicted) at each time of measurements after challenge. No significant correlations were found. One symbol for each subject. BC: before challenge; 0: immediately after challenge; 0.5: 0.5 h after challenge; 2.5: 2.5 h after challenge; 5 h after challenge.
change in FEV₁ in another patient (fig 2). The relation between FEV₁ and log SDQ could also change in one patient when comparing immediate and late phase reactions. For example, immediately upon challenge patient no. 3 (fig 1) showed a clear VA/Q mismatch and a low FEV₁. After 5 hours log SDQ was within the normal range despite the same reduction in FEV₁ as earlier. By contrast, patient no. 1 showed a small decrease in FEV₁ and a clear VA/Q mismatch after 5 hours in contrast to a more reduced FEV₁ and a normal log SDQ immediately after challenge. A slower return of log SDQ against baseline compared to FEV₁ was seen in 7 of the 8 patients.

Discussion

Gas exchange after allergen challenge

The present study documents the development of pulmonary gas exchange impairment following allergen challenge with both immediate and late phase reaction. All patients showed a broader distribution of the perfusion and different VA/Q ratios (increased log SDQ) and some patients also showed a more or less separated mode of perfusion to regions with low VA/Q.

The degree of gas exchange impairment immediately after challenge (log SDQ 0.73) was of the same magnitude as that found in patients with chronic stable, moderate non-allergic asthma (mean 0.74) [2]. However, it was slightly lower than reported in patients during exercise-induced asthma [12] or in those after being challenged with methacholine [3]. Patients with acute severe asthma showed even higher log SDQ (mean 1.34) and in 9/10 patients a bimodal distribution of the perfusion was found [13]. In the other quoted studies as well as in the present study, a bimodal distribution developed but only in a few patients. Thus, bimodal perfusion distribution appears in all kinds of asthma, especially in severe asthma. The pattern with perfusion to areas with low VA/Q ratios besides normal VA/Q ratios has also been seen in patients with advanced chronic obstructive airways disease with severe cough and sputum [14].

A late phase reaction is typical for allergen challenge and in this phase too, gas exchange mismatch was characterized by a broad and sometimes bimodal distribution of the perfusion with additional low VA/Q. The degree of VA/Q inequality during the late phase reaction was not possible to predict from the degree of VA/Q mismatch immediately upon challenge. Somewhat surprising was the finding that 2 patients with a late phase reaction (low FEV₁) did not show any gas exchange mismatch suggesting a dominating central airways spasm and less change in peripheral airways.

Although a ventilation-perfusion mismatch was seen in all patients, no pronounced shunt developed with the provocation. The absence of shunt, even in severe asthma, but the presence of a distinct low VA/Q mode, has been suggested to be due to collateral ventilation, maintaining some gas exchange in otherwise closed lung regions [1, 14].

Gas exchange and forced expiratory flow

An interesting observation is the dissociation between the time courses of FEV₁ and log SDQ after challenge. In 7 of the 8 patients log SDQ showed a slower return to baseline values than FEV₁. Similar dissociation in the time courses has also been seen during the recovery period of acute severe asthma, even if the time perspective was different [13] and after methacholine challenge [3]. Dissociation between the time courses of gas exchange (log SDQ) and airway resistance was also seen in a rabbit model after methacholine challenge [15]. In contrast, in exercise-induced asthma [12] gas exchange abnormalities appear to recover before spirometry, suggesting a different pathophysiological mechanism. Low or no correlation between forced expiratory flow and VA/Q mismatch has also been shown in the first period after hospitalization in patients with acute severe asthma [13], and after exercise induced asthma [12].

Both the dissociation of the time courses and the low correlation between ventilation-perfusion matching and forced expiratory flow indicate that these two manifestations of asthma have different pathophysiological backgrounds or, at least, that pathophysiological events other than bronchoconstriction influence the gas exchange after allergen challenge. Thus, the present study shows that the reaction after allergen challenge is also compatible with the hypothesis that reduced forced expiratory flow reflects widespread bronchoconstriction in the bronchial tree, whereas gas exchange impairment is related to preferential inflammatory peripheral airways (mucus and/or oedema). The complexity of the asthma disease is also stressed by the findings of poor correlations between forced expiratory flow and breathlessness, and between VA/Q mismatch and breathlessness.

Also, when looking at an individual patient the relation between forced expiratory flow and VA/Q inequality could vary between the immediate and late phase reaction. In five patients there were slight but significant correlations between log SDQ and FEV₁ over the whole study period. However, the large variation in the slope coefficient precluded the calculation of log SDQ from FEV₁, or vice versa, for the group as a whole. Moreover, the varying and weak correlations need not imply that the bronchoconstriction (registered by a decreased FEV₁) caused the gas exchange mismatch, but rather that airflow and gas exchange varied in parallel. In view of the large interindividual and intrindividual variations in log SDQ it should be stressed that only a minor fraction of the variation (approximately 8.6%) is accountable to methodological error as assessed in a previous study [16].
In summary, during both the immediate phase reaction and the late phase reaction the pattern of \( V_{A}/Q \) mismatch after antigen challenge was similar to that found in other studies on asthma. A broad distribution of perfusion and, sometimes, regions of modest low \( V_{A}/Q \) were seen. There was a poor relationship (both interindividual and intraindividual) between forced expiratory flow and gas exchange mismatch indicating different pathophysiological mechanisms for reduction of forced expiratory airflow rates and gas exchange impairment.

Acknowledgements: The writers thank Harrieth Gustavsson and Caroline Angleryd for their skilful technical assistance.

References


