Diagnosis and treatment of patients with progressive airflow obstruction

Edward Dompeling
Diagnosis and treatment of patients with progressive airflow obstruction

A long-term study in general practice

Een wetenschappelijke proeve
op het gebied van de medische wetenschappen
in het bijzonder de geneeskunde

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<td>AD-FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Annual decline in FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<tr>
<td>BDP</td>
<td>Beclomethasone dipropionate</td>
</tr>
<tr>
<td>BDR-FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Bronchodilating response in FEV&lt;sub&gt;1&lt;/sub&gt;, expressed as a percentage of the predicted value of FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>BHR</td>
<td>Bronchial hyperresponsiveness</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CV</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>CV-PEFR</td>
<td>Week-to-week coefficient of variation of the PEFR</td>
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<tr>
<td>DI-PEFR</td>
<td>Diurnal PEFR index</td>
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<tr>
<td>d.p.i</td>
<td>Dry powder inhalation</td>
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<tr>
<td>ECSC</td>
<td>European Coal and Steel Community</td>
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<td>EVC</td>
<td>Slow expiratory vital capacity</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;%pred</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; as a % of the predicted value</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;-pre</td>
<td>Prebronchodilator FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;-post</td>
<td>Postbronchodilator FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;-pred</td>
<td>Predicted value of FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>ΔFEV&lt;sub&gt;1&lt;/sub&gt;-max</td>
<td>Maximal absolute response (postbronchodilator minus prebronchodilator value) in FEV&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;-max</td>
<td>Maximal postbronchodilator value</td>
</tr>
<tr>
<td>FIV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced inspiratory volume in one second</td>
</tr>
<tr>
<td>FPD</td>
<td>Fast progressive disease</td>
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<td>FRC</td>
<td>Functional residual capacity</td>
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<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>G</td>
<td>Gain</td>
</tr>
<tr>
<td>ΔG%</td>
<td>Percentage difference between largest and smallest gains</td>
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<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>IB</td>
<td>Ipratropium bromide</td>
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<tr>
<td>ISH</td>
<td>Inventory of subjective health</td>
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<tr>
<td>IVC</td>
<td>Inspiratory vital capacity</td>
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<tr>
<td>L</td>
<td>Litre</td>
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<tr>
<td>MANOVA</td>
<td>Multiple analysis of variance</td>
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<tr>
<td>MEF&lt;sub&gt;50&lt;/sub&gt;</td>
<td>Maximal expiratory flow rate at 50% of FVC</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<td>NHP</td>
<td>Nottingham Health Profile</td>
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<td>PC_{20}</td>
<td>Provoking concentration of histamine producing a 20% fall in FEV&lt;sub&gt;1&lt;/sub&gt;</td>
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<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume</td>
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<tr>
<td>S</td>
<td>Salbutamol</td>
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<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SPD</td>
<td>Slowly progressive disease</td>
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<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>T_{l}/V_{a}</td>
<td>Transfer coefficient</td>
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<td>VC</td>
<td>Vital capacity</td>
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Aan God
1. General introduction

1.1. Introduction

Both asthma and Chronic Obstructive Pulmonary Disease (COPD) can be regarded as chronic, progressive disorders of the airways (1-5), with a prevalence of 10-20 per 1,000 in The Netherlands and other countries in Europe (6,7). Asthma can occur in all age groups, although it is particularly a disease of the young. The most common symptoms of asthma are wheezing, dyspnoea, chest tightness, cough, and sputum production. Characteristic is a history of recurrent exacerbations (or attacks) often provoked by exogenous factors such as allergens, irritants, exercise, and virus infections. Nocturnal and early morning asthma symptoms are particularly characteristic (3,8). Bronchial hyperresponsiveness to nonspecific stimuli like cigarette smoke, fog, perfume, exercise and cold air is present and is a hallmark of asthma. Asthma is nowadays regarded as an inflammatory disorder of the airways in which many cells play a role, including mast cells and eosinophils (8-10). Inflammation of the airway wall is related to bronchial hyperresponsiveness and to variability of airway obstruction.

COPD characteristically affects middle-aged and older patients. Patients with COPD mostly have dyspnoea which is often accompanied by cough, wheezing, sputum, and recurrent respiratory infections (3). COPD comprises three disorders: emphysema, peripheral airway disease and chronic bronchitis. Any individual patient may have one or more or all of these conditions, but the dominant feature in COPD is the permanent limitation of expiratory airflow. Nonspecific bronchial hyperresponsiveness can be present but is less common than in asthma (11). Long-term use of cigarettes is one of the principal identified causes of COPD. However, the above disorders do not occur solely in cigarette smokers, nor does the majority of cigarette smokers develop clinically manifest COPD (3).

In the Netherlands, Orie et al. developed a hypothesis about the origin and development of ‘chronic non-specific lung disease (CNSLD)’, which later became known as the ‘Dutch hypothesis’ (12). They proposed that a common genetic host factor predisposes to bronchial hyperresponsiveness and allergy which in connection with exposure to smoke, allergens and other environmental irritants may induce chronic airway obstruction. Defined in this way, ‘asthma’, ‘asthmatic bronchitis’, ‘chronic bronchitis’ or ‘COPD’ may have a comparable pathogenetic mechanism although the emphasis may be on different factors (12,13). The various views were recently discussed (13,14). So far, it is a hypothesis under study which has neither been refuted, nor proven. The pathogenetic mechanisms have only partly been revealed today. In this thesis, patients with asthma have been discriminated from those with COPD on
the basis of the standards for diagnosis of the American Thoracic Society (3). 'Chronic bronchitis', 'chronic airflow limitation' and 'COPD' are used as synonyms in this thesis.

In the treatment of asthma and COPD, two main classes of drugs can be identified: bronchodilators (beta-adrenergic agonists, anticholinergics or theophyllines) and anti-inflammatory drugs (corticosteroids, sodium cromoglycate or nedocromil) (3,10). Bronchodilators are believed to act primarily by reversing or inhibiting the contraction of airway smooth muscle, although they may have additional properties (10). Corticosteroids are anti-inflammatory drugs, of which the exact mechanisms of action are not fully understood. They probably inhibit and decrease inflammation on various levels. They are (possibly) important in preventing migration, activation and release of all kinds of mediators of inflammatory cells (8,10).

There are indications for a world-wide increase in morbidity and mortality due to asthma and COPD in the last two decades (15-17), although differences exist between countries (18). This increase may not be present in the Netherlands (19). It is possible that continuous (mono)therapy with bronchodilators is to some extent related to this world-wide increase in morbidity and mortality (20). Data to support this concept come from several retrospective studies (21-24) and from two prospective ones (25,26). Following some earlier case control studies from New Zealand, Spitzer et al. investigated the relationship between the use of all kinds of bronchopulmonary medications and the risk of death or near-death episodes in asthma (24). An increased, even dose-related risk was found, not only for the beta2-agonist fenoterol but also for the other beta2-agonists and theophyllines. No increased risk was found for the anti-inflammatory agents sodium cromoglycate and inhaled corticosteroids. In a prospective study of 89 stable asthmatics, Sears et al. found a poorer control of asthma during regular use of fenoterol for six months than during therapy on demand (26). In the two-year randomized controlled study of our own group, the effects of bronchodilators on the course of asthma and COPD was assessed in 223 patients selected from general practice (25,27). Two important aspects of the treatment of asthma and COPD with bronchodilators alone were found: a) a relatively large group of patients had an unexpectedly rapid progression of asthma or COPD (in terms of annual decline in lung function and frequency of exacerbations), and b) continuous bronchodilator treatment as monotherapy was accompanied by a more rapid annual decline in lung function than treatment on demand.

The main questions of our follow-up study in this group (and of this thesis) therefore are:
1) How can we identify patients who have a rapid progression of asthma or COPD? 
2) Does treatment with inhaled corticosteroids decelerate this rapid progression of asthma or COPD in these patients?

To answer the second question, a group of 56 patients with a relatively rapid progression of their disease during bronchodilator therapy alone was selected for two-year additional treatment with an inhaled corticosteroid (beclomethasone dipropionate 400 μg, two times daily).

It is possible that in the past too much emphasis was put on bronchodilator therapy.
alone) rather than on anti-inflammatory therapy with inhaled corticosteroids, sodium cromoglycate and nedocromil (10). Three recent reports on the treatment of asthma have proposed anti-inflammatory treatment with inhaled corticosteroids as an important, first-line therapy of asthma (8,10,28). Although there is ample evidence for the short-term efficacy of inhaled steroids in asthma, hardly any data are available of the effects during one or more years. In patients with COPD, there is controversy about the treatment with corticosteroids (29). Several short-term studies of some weeks to some months reported beneficial effects of corticosteroids in COPD (30-32), whereas others observed no significant effects (29,33-34). Two retrospective, uncontrolled studies during several years suggested that corticosteroids might slow down the decline in lung function in COPD patients with moderately severe and severe airway obstruction (35,36). A preliminary report of a two-year prospective controlled study in 58 male patients with chronic airflow obstruction suggested that inhaled budesonide was able to reduce the annual decline in lung function in these patients (37). Long-term studies with inhaled corticosteroids during several years are urgently needed in both patients with asthma and COPD in order to establish the place of inhaled corticosteroids in the treatment of these diseases (8,38).

In the past few years, two other long-term trials with inhaled corticosteroids have been carried out in the Netherlands, one in children with asthma, the other in adults with obstructive airway disease. The main results suggest beneficial effects of inhaled corticosteroids on lung function, bronchial hyperresponsiveness, symptoms and exacerbations (39,40).

The questions of our follow-up study are very much related to the early diagnosis and early treatment of patients with asthma or COPD in general practice. Underdiagnosis and undertreatment of asthma and COPD have been reported several times in general practice (41-44). Most patients with asthma or COPD in the Netherlands and other countries are treated in general practice (45,46), which stresses the importance of the subject. In general, it is the difficult task of the general practitioner to identify the patients at risk, which in the case of asthma and COPD implies detecting patients with a large decline in ventilatory function. These patients run the risk of early disability or death from chronic airway obstruction (1,47). The question is if the general practitioner can trace these patients in an early stage of their disease with diagnostic parameters like respiratory symptoms, physical signs of the chest and peak-flow rate (Chapter 4). Perhaps supplementary instruments like a FEV1 meter are necessary in order to make a better assessment of airway obstruction and monitoring of the disease process possible. It is not clear whether the electronic spirometers available nowadays are reliable enough for use in general practice (48). An assessment of the reliability of the integrating Microspiro HI-298 flow meter is described in Chapter 2. The reversibility of airway obstruction as assessed by the increase in lung function after the administration of a bronchodilator is an important predictor of the course and prognosis of patients with asthma and COPD (1). However, it is unclear how reversibility is best expressed: as absolute increase, as a percentage of the initial lung function value or predicted lung function value, etc. (49). In Chapter 3, we have investigated which way of expressing reversibility is most reproducible and least dependent on the prebronchodilator lung function. Another question is whether patients
with bronchial hyperresponsiveness should be identified by the general practitioner or not. It has been suggested that bronchial hyperresponsiveness to nonspecific stimuli is an important risk factor for the annual decline in lung function (2,4,50,51). However, it is also possible that bronchial hyperresponsiveness is not a 'cause' but a 'consequence' of the loss in lung function (50). In Chapter 5, we tested the hypothesis that bronchial hyperresponsiveness is a 'cause' of airway obstruction in asthma but a 'consequence' of airway obstruction in COPD.

Early detection of patients at risk is only useful when early intervention is possible and effective. Corticosteroids may be the most effective therapy of asthma and COPD currently available. However, relatively little is known about the long-term effects of these drugs during one or more years (8,38). Do inhaled corticosteroids prevent the loss of lung function during several years (52)? Once an excessive loss in lung function has occurred, an important therapeutic question is whether inhaled corticosteroids are able to restore the loss in lung function. The capacity of inhaled corticosteroids to decelerate the deterioration of asthma and COPD during bronchodilator therapy alone has been described in Chapters 6 and 7. We also analysed which patients with asthma or COPD in particular benefit from long-term treatment with inhaled corticosteroids. This analysis is described in Chapter 8. Although the short-term effects of steroids on objective parameters like lung function and bronchial hyperresponsiveness are well-known (particularly in asthma), no studies are known about the effects of inhaled corticosteroids on the subjective well-being (quality of life) of patients with asthma and COPD. We assessed the influence of an inhaled corticosteroid on quality of life in patients with asthma and COPD (Chapter 9). A problem for the long-term efficacy of inhaled corticosteroids is patient-compliance and inhaler technique (53). In contrast to bronchodilators, the prophylactic corticosteroids do not have a direct symptom-relieving effect (10). Therefore, patients may not notice improvements in e.g. lung function, induced by corticosteroids. This may reduce patient compliance with the inhaled corticosteroids, particularly when used for several years. Long-term patient compliance with and inhaler technique of an inhaled corticosteroid in asthma and COPD has been described in Chapter 10. Another very important question regarding the long-term treatment with inhaled corticosteroids concerns the possibility of stopping when patients are in a clinically stable phase of disease (54). The answer to this question has to do with fundamental aspects of steroid action: do steroids merely suppress the disease temporarily or do they really 'cure' asthma or COPD to some extent? If steroids are merely acting as suppressors, treatment with these medicines can not be discontinued. If long-term treatment with these drugs does 'cure' asthma or COPD to some extent, therapy with steroids can be interrupted. Chapter 11 describes the results of stopping treatment with inhaled corticosteroids in asthma and COPD.

1.2. Aims of the thesis

The aim of this thesis is to answer the following questions with respect to diagnosis and treatment of asthma or COPD:
**Diagnosis**

a. Is the portable, integrating Microspiro HI-298 flow meter a reliable instrument for use in general practice? *(Chapter 2)*.
b. Which way of expressing the immediate bronchodilating response is most reproducible and least dependent on the prebronchodilator lung function? *(Chapter 3)*.
c. Is it possible to detect patients at risk (with a large decline in lung function and a high exacerbation rate) on the basis of a single cross-sectional assessment of lung function, respiratory symptoms, quality of life, allergy and physical signs of the chest? *(Chapter 4)*.
d. Is bronchial hyperresponsiveness a ‘cause’ or a ‘consequence’ of airway obstruction in asthma or COPD? *(Chapter 5)*.

**Treatment**

e. Does treatment with inhaled corticosteroids decelerate the deterioration of asthma or COPD during bronchodilator therapy alone? *(Chapters 6 and 7)*.
f. Which clinical characteristics in asthma and COPD can predict the two-year response to an inhaled corticosteroid? *(Chapter 8)*.
g. Does treatment with inhaled corticosteroids improve the quality of life in patients with asthma or COPD? *(Chapter 9)*.
h. How good is long-term compliance with and inhaler technique of an inhaled corticosteroid in patients with asthma and COPD? *(Chapter 10)*.
i. What is the course of asthma and COPD after stopping maintenance treatment with inhaled corticosteroids? *(Chapter 11)*.

**1.3 Outline of the study**

**Patient selection**

29 General practitioners were asked to select all their patients aged 30 and over with symptoms of asthma or COPD *(25,44)*. Only those patients who showed moderate airway obstruction *(FEV₁ or FEV₁/EVC had to be two standard deviations below their predicted value*(55)*), but higher than 50% of the predicted value) and/or bronchial hyperresponsiveness to histamine *(PC₂₀ ≤ 8 mg/ml)* were included by the investigators. Exclusion criteria were: dependence on corticosteroids, chronic heart failure, malignant disorders or other severe, life-threatening diseases. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.

**Part one**

Patients were randomly allocated to two parallel treatment groups *(25)*:

1. continuous bronchodilator treatment of salbutamol 400 µg or ipratropium bromide 40 µg, four times daily (dry powder inhalations)
2. bronchodilator treatment ‘on demand’ during periods of dyspnoea or exacerbations with dry powder inhalations of salbutamol 400 µg or ipratropium bromide 40 µg.
Within these parallel groups, a cross-over comparison was made between salbutamol and ipratropium bromide: patients used each drug for one year. The order of the drugs was determined at random. In an eight-week wash-out period before the start of the study, bronchopulmonary medication other than the trial medication was stopped (corticosteroids, sodium cromoglycate, theophylline, etc).

Part two
56 Patients with an unfavourable course of disease (an annual decline in FEV₁ of at least 80 ml/yr in combination with at least two exacerbations/yr) during treatment with bronchodilators alone (part one of the study) were selected for additional treatment with inhaled beclomethasone dipropionate (BDP).

During the third and fourth year, the 56 patients were additionally treated with BDP 400 μg two times daily in combination with salbutamol 400 μg or ipratropium bromide 40 μg four times daily (all dry powder inhalations). The bronchodilator inhaled during the second year was also used in the third and fourth year.

Once every three months, proper inhalation technique as well as compliance with the prescribed medication were checked. Patients were instructed to rinse their mouth after the dry powder inhalations.

Study design

![Diagram showing study design]

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2. Accuracy, precision and linearity of the portable flow-volume meter Microspiro HI-298*

Abstract
The accuracy, precision and linearity of a new portable flow volume meter, the Microspiro HI-298® (Chest Corporation, Tokyo, Japan), was investigated using a Fleisch no 4 pneumotachograph as a standard. After connection and calibration of the pneumotachograph and the Microspiro, a healthy subject performed 44 forced vital capacity (FVC) manoeuvres at different levels of lung inflation. The FVC of these expirations ranged from 2.5 to 5.1 litres. Linear regression of Microspiro values (dependent variable) on Fleisch pneumotachograph values (independent variable) showed that a good linear relationship existed. Pearson correlation coefficients ranged from 0.938-0.985. Linearity of the Microspiro was good except for the peak-flow rate (PEFR) and the maximal expiratory flow at 25% of expired volume (MEF25). The random error (measure of precision) of all flow-volume (F-V) indices was lower than 5%. The systematic error (measure of accuracy) was low for the forced expiratory volume in one second (FEV1) and the FVC (1.0% and 4.6% respectively) but much higher for the instantaneous expiratory flows (PEFR 11.0%, MEF75 7.0%, MEF50 8.5%, MEF25 11.4%).

Only the total error in FEV1 complied with the tolerance of 4% of the European Coal and Steel Community (ECSC). When the measured values were adjusted according to the regression equations of this study, all F-V indices were accurate and precise within 5%.

It was concluded that the portable Microspiro HI-298® is a useful instrument for bedside, work-site spirometry and for use in General Practice. As the accuracy of the instantaneous expiratory flows (PEFR, MEF75, MEF50 and MEF25) is moderate, it is advised to adjust these values with the regression equations of this study.

2.1. Introduction
The forced expiratory manoeuvre is a widely used method for assessing the degree of airflow obstruction in patients with asthma and Chronic Obstructive Pulmonary Disease (COPD). It is well-known that the variability of flow-volume (F-V) indices is rather high (1-3). One of the sources of variability is the random error of the instrument by which the F-V parameters are measured (4). Therefore, both the American Thoracic Society (ATS) and the European Coal and Steel Community (ECSC) formulated extensive recommendations on the accuracy and precision of spirometers in order to improve the quality of the F-V data (5-7). As a number of tested devices appeared to be inadequate (8,9), it was advised to test new available spirometers (10,11). During the past few years the need for simple but reliable spirometers for bedside, work-site spirometry and for use in general practice has been rising. A promising instrument in this field may be the portable Microspiro HI-298® (Chest

Corporation, Tokyo, Japan). It is a very compact, light apparatus with useful possibilities. Although the Microspiro is widely used, the reliability has not been tested. Therefore this study intends to investigate the accuracy, precision and linearity of the Microspiro.

2.2. Methods

Instrument
The Microspiro HI-298® is produced by the Chest Corporation, Tokyo, Japan. Figure 2.1 shows a schematic drawing of this portable flow-volume meter. The apparatus measures instantaneous flows which are integrated electronically into volumes. The following indices are measured: slow expiratory vital capacity (EVC), forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), peak expiratory flow rate (PEFR), maximal expiratory flows at 25%, 50% and 75% of the expired volume (MEF₇⁵, MEF₅₀, MEF₂⁵ respectively). The measured values, predicted values, and measured values as percentages of predicted values are shown on a liquid crystal display together with a spirogram and a F-V curve. The two best efforts (the FVC-manoeuvres with the largest sum of FEV₁ and FVC (6)) are stored in the memory and can be printed. The print-out takes 2-3 minutes. The predicted values are based on the equations of the ECSC for adults (5) and of Dickman et al. (12) or Zappetal et al. for children (13). It is possible to adjust the predicted volume values for different ethnic groups. Measured values are body temperature and pressure saturated (BTPS) corrected. The bronchodilator responsiveness is automatically calculated, as the instrument stores prebronchodilator values and compares them with data after bronchodilatation. The warming-up takes five minutes. The Microspiro has a flow range of 0 to 14 l/s. The volume range is 0.4 to 8.0 liters. The measurement time for a FVC-manoeuvre takes 18 seconds at most. These specifications are in accordance

Figure 2.1 A schematic drawing of the Microspiro HI-298®
with the standards of the ATS and the ECSC (5-7). The Microspiro HI-298 is a forced oscillatory flow meter (14). It contains a swirl sensor (15). The sensing technique of this meter is based on a relatively new method of measuring flows (14,15). A set of stationary swirl blades forces gas entering the swirl meter to spin around the central axis of the meter, forming vortices. The vortices advance through the meter like screws. The frequency of the vortices shows a linear relationship with the velocity of the gas. A sensor probe in the meter senses the passage of these vortices. The sensor in the meter is a thermistor (a resistor which changes its resistance with temperature). A constant current passes the thermistor causing the device to heat. The gas passing along the thermistor removes heat. As the velocity of the gas changes when a vortex passes along the thermistor the heat removal from the thermistor also changes. In this way each vortex is accompanied by resistance change in the sensor. As a constant current passes through the sensor the voltage across the sensor varies as each vortex passes. This change of voltage is AC coupled into the electronic system and after suitable processing is counted and interpreted as flow velocity. An advantage of the Microspiro is that it does not sample flows but measures the whole flow stream. It is known that through sampling of flows or volumes large errors can result (7,10).

Experiment
The Microspiro was connected in series with a standard instrument, the Fleisch no.4 pneumotachograph (4,16). The maximal error of the Fleisch pneumotachograph is not more than 3% (16). Up to a flow of 11 l/s the linearity of a type 4 Fleisch pneumotachometer was shown to be good (16). The Fleisch pneumotachometer was a commercial type: Discom -21®, Chest Corporation, Tokyo, Japan. The transducer (5 cm ID) is heated to 37 degrees. At both sides of the transducer, a conical attachment ensures a laminar flow through the transducer. The pneumotachometer measures instantaneous flows which are integrated electronically into volumes. At the start of the experiment, the pneumotachograph (in series with the Microspiro) was calibrated with a one litre syringe. A healthy subject performed 44 forced expirations through the connected instruments at different levels of lung inflation. The FVC of these expirations ranged from 2.5 to 5.1 litres. Paired data were taken for the FVC, FEV1, PEFR and MEF-values. Linear regression analysis was applied to the paired data, in which the Fleisch values were the independent variables and the Microspiro values the dependent variables. The distance from the line of identity to the regression line, \(M=a.F+b\) (\(M=\) Microspiro value, \(F=\) Fleisch value, \(a=\) regression coefficient and \(b=\) the intercept), was defined as systematic error, which is a measure for the accuracy of the instrument (17). For all F-V parameters except the PEFR the regression lines went through the origin (\(b=0\)). In this case the systematic error in % is given by a constant: \((a.F/F).100\%=100.a\%\). In the case of the PEFR a mean systematic error was calculated. The deviation of Microspiro values from the regression line was defined as the random error, which is a measure for the precision of the Microspiro (17). The random error in % was calculated by determining the % variance which was not explained by the model \((=1-r^2).100\%\) in which \(r=\) Pearson correlation coefficient) (17,18). The total error was defined as systematic error.
Linearity was assessed in the following way. First the gain (G) of the system was calculated by dividing Microspiro values by the corresponding Fleisch values (G=Microspiro value/Fleisch value) (16). The percentage difference between the largest and smallest gains (ΔG%) in a specified flow or volume range is a measure for the linearity of the system (16,19).

2.3. Results and discussion

A good linear relationship was found between the Fleisch pneumotachograph values and the Microspiro values for all F-V indices (Table 2.1 and Figure 2.2). Pearson correlation coefficients ranged from 0.938 to 0.985 (Table 2.1). The ΔG% of F-V indices was lower than 10% (except for the PEFR and the MEF75), indicating that the linearity of most F-V indices (FVC, FEV1, MEF50 and MEF25) was good. The Microspiro gave systematic over-readings for the FVC, systematic under-readings for the other F-V indices. The systematic error ranged from 1.0% for the FEV1 (good accuracy) to 11.4% for the MEF25 (low accuracy). The random error of all indices was within the 5% limit advised for spirometry (10). However, only the FEV1 had a total error within the tolerance limits of 4% of the ECSC (5). Therefore, the portable Microspiro is a reliable meter for measuring the FEV1 but it is less accurate in measuring instantaneous forced expiratory flows (PEFR, MEF75, MEF50 and MEF25). However, the accuracy can be increased by adjusting the values according to the linear regression equations of this study (Table 2.1). With these adjustments the total error of all F-V indices will be lower than 5%. As the swirl sensor itself probably is accurate and linear within 1% (14,15), the manufacturer may change the electronic amplifier and signal conditioner. These parts of the electronic system are the links where the sources of error may exist. The Microspiro can be used in general practice, for bedside and work-site spirometry and for epidemiological purposes. The automatic calculation of the reversibility of bronchial obstruction (in percentages of the initial FEV1) is a convenient additional feature. Because of the moderate accuracy of the instantaneous expiratory flow rates, it is advisable to use the adjusted values.

Table 2.1 The regression lines, values of total error (systematic error ± random error), linearity (ΔG%) and Pearson's correlation coefficients (r) of six F-V indices. The intercept of PEFR is given in litre/second. The standard errors are given between parentheses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regr.coefficient</th>
<th>Intercept</th>
<th>r</th>
<th>Error (%)</th>
<th>ΔG%</th>
</tr>
</thead>
</table>
| FVC      | 1 045 (0 007)    | -         | 0.978 | + 4.6±4.3 | 8.5  
| FEV1     | 0 990 (0 007)    | -         | 0.985 | - 1.0±3.0 | 9.5  
| PEFR     | 0.794 (0.029)    | 0.698 (0.204) | 0.975 | -11.0±5.0 | 39.6 
| MEF75    | 0.930 (0.009)    | -         | 0.981 | - 7.0±3.9 | 16.7 
| MEF50    | 0.915 (0.008)    | -         | 0.982 | - 8.5±3.6 | 1.9  
| MEF25    | 0.896 (0.017)    | -         | 0.938 | -11.4±3.9 | 1.6  

1 range of FVC and FEV1 1 - 4 litres, 2 range of PEFR 15 - 10 litre/sec, 3 range of MEF-values 1 - 8 litre/sec
It was concluded that the Microspiro HI-298® only gives reliable values for the FEV₁. However, when the measured values of the other F-V indices are corrected with the regression equations of this study, all values will be accurate and precise within 5%.

References


3. A comparison of six different ways of expressing the bronchodilating response in asthma and COPD

Reproducibility and dependence on prebronchodilator FEV₁*

Abstract

Various indices are used to express the bronchodilating response. It is unclear, however, which index is most informative. The aim of this study was to compare six expressions of the bronchodilating response and to examine 1) the independence of the prebronchodilator forced expiratory volume in one second (FEV₁), and 2) the reproducibility of the bronchodilating response. Bronchodilating responses (increases in FEV₁ 60 minutes after salbutamol 400 μg and ipratropium bromide 80 μg) on six test occasions, during two years, of 183 patients (72 asthma, 111 COPD) from a large bronchodilator intervention study were used. The dependence of the prebronchodilator FEV₁ was investigated both between-patients (cross-sectional analysis) and within-patients (longitudinal analysis) by means of linear regression analysis. The reproducibility of the bronchodilating response was calculated by means of the coefficients of variation (CVs) of the six bronchodilating responses during two years. The CVs of the six expression indices were compared by analysis of variance (ANOVA).

The results showed that no index was independent of the prebronchodilator FEV₁. However, some indices were significantly more dependent of the prebronchodilator lung function and, therefore, less reproducible than others. The '% initial' index (change as a percentage of the prebronchodilator value) was the most dependent of the prebronchodilator lung function and had the worst reproducibility (CV ranged from 50-61%). The '% possible' (change as a percentage of the predicted minus prebronchodilator value) and '% achievable' (absolute change as a percentage of the maximal postbronchodilator minus prebronchodilator value) indices were the least dependent of the prebronchodilator value and had the highest reproducibility (CV ranging from 34-53%).

The way in which bronchodilating responses should be expressed depends on the purpose of the test. It was concluded that the '% initial' index was most dependent of the prebronchodilator FEV₁ and had the worst reproducibility, whereas for the '% possible' or '% achievable' indices the opposite was found. In bronchodilator studies, the latter expression indices increase the possibility of detecting differences in bronchodilating efficacy between different drugs.

3.1. Introduction

Assessment of the responsiveness to bronchodilators in patients with airway obstruction is a test often used in clinical and experimental situations (1). The bronchodilating response, mostly assessed by the increase in forced expiratory volume in one second (FEV₁), provides objective information about the degree of reversibility of airway obstruction (2) and the response to different types of drugs (3). Various indices are used to express the response to bronchodilators: absolute change (4-6) and absolute change as a percentage of the prebronchodilator value (7,8), of the predicted value (5,9), of the maximal response (10), of the maximal postbronchodilator minus

prebronchodilator value (10,11) or of the predicted minus prebronchodilator value (12). It is not clear, however, which method of expressing the bronchodilating response is most informative (1,13). Particularly in asthma, marked fluctuations in pulmonary function may occur both throughout the day and from day-to-day (14,15). As a consequence, the bronchodilating response may fluctuate correspondingly, which may lower the comparability of responses both between- and within-subjects. The use of an index independent of the prebronchodilator FEV₁ and with reproducible values may generally be most appropriate (13). It is not clear which index (if any) for expressing reversibility has these properties. Two cross-sectional studies on this subject led to contradicting results. Postma et al. (16) observed that the ‘% possible’ index (absolute change as a percentage of the predicted minus prebronchodilator value) was independent of the prebronchodilator lung function. Weir and Burge (13) claimed that not ‘% possible’ but ‘% predicted’ (change as a percentage of the predicted value) was independent of the prebronchodilator lung function. However, these findings were based on a single cross-sectional assessment in patients with non-asthmatic chronic airway obstruction in which reversibility of obstruction and fluctuations of pulmonary function are not ‘characteristic’.

In a prospective controlled study, during two years, in both asthma and Chronic Obstructive Pulmonary Disease (COPD), we investigated which bronchodilator index was independent of the prebronchodilator FEV₁ and compared the reproducibility of six indices for expressing reversibility. Data on six bronchodilating responses, during two years, of 183 patients participating in a bronchodilator intervention study were used for this purpose (17,18).

3.2. Methods

Patients

An extensive description of patient selection, in- and exclusion criteria of the bronchodilator intervention study was given previously (17,18). In summary: 29 general practitioners in the catchment area of the University of Nijmegen were asked to select all their patients aged 30 and over with symptoms of asthma or COPD. Only patients who showed mild to moderate airway obstruction (FEV₁ ≥50% of the predicted value (19)) and/or increased bronchial responsiveness to histamine (provoking concentration of histamine that produces a 20% fall in FEV₁ (PC₂₀) ≤8 mg/ml) were included by the investigators. The diagnosis of asthma or COPD was based on the criteria of the American Thoracic Society (ATS)(14). Asthma was defined as the combination of (17,18): 1. reversible obstruction (increase in FEV₁ one hour after the administration of 400 μg salbutamol and 80 μg ipratropium bromide ≥15% of the prebronchodilator value); 2. bronchial hyperresponsiveness to histamine (PC₂₀ ≤8 mg/ml); 3. dyspnoea; 4. allergy (at least one positive test out of seven radio-allergosorbent tests (RAST) (Pharmacia, Sweden. Pollen: weeds, grasses, trees; animals: cats and dogs; house dust mite; Aspergillus Fumigatus)) and/or wheezing.

COPD was defined as the combination of (17,18): 1. chronic cough or chronic sputum production for at least three months during at least two consecutive years; 2.
continuous airway obstruction (FEV\textsubscript{1} less than 85% of the predicted value). Patient characteristics are shown in Table 3.1. The study was approved by the University Ethics Committee. All patients gave informed consent.

Table 3.1 Clinical characteristics of patients with COPD and asthma. Data are presented as mean values with SD in parentheses. Differences between patients with asthma and those with COPD are tested by means of a chi-square test (dichotomous variables) or unpaired Student's t-test (continuous variables).

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>111</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>53 (13)</td>
<td>51 (13)</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smokers (+/-)</td>
<td>67/44</td>
<td>27/45</td>
<td>0.003</td>
</tr>
<tr>
<td>Pack years</td>
<td>19 (17)</td>
<td>13 (16)</td>
<td>0.015</td>
</tr>
<tr>
<td>Allergic (+/-)#</td>
<td>20/89</td>
<td>25/46</td>
<td>0.011</td>
</tr>
<tr>
<td>FEV\textsubscript{1} (L)</td>
<td>2.44 (0.82)</td>
<td>2.18 (0.77)</td>
<td>0.039</td>
</tr>
<tr>
<td>FEV\textsubscript{1} %pred</td>
<td>77 (18)</td>
<td>73 (20)</td>
<td>0.19</td>
</tr>
<tr>
<td>FEV\textsubscript{1-maxpost} (L)</td>
<td>2.81 (0.83)</td>
<td>2.77 (0.84)</td>
<td>0.80</td>
</tr>
<tr>
<td>VC (L)</td>
<td>3.60 (1.03)</td>
<td>3.53 (1.06)</td>
<td>0.66</td>
</tr>
<tr>
<td>VC %pred</td>
<td>90 (16)</td>
<td>92 (18)</td>
<td>0.39</td>
</tr>
<tr>
<td>VC-maxpost (L)</td>
<td>3.95 (1.01)</td>
<td>3.95 (1.06)</td>
<td>0.99</td>
</tr>
<tr>
<td>Reversibility in FEV\textsubscript{1}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘absolute’ (L)</td>
<td>0.26 (0.14)</td>
<td>0.46 (0.27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>‘% initial’</td>
<td>13 (9)</td>
<td>25 (16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>‘% predicted’</td>
<td>8 (4)</td>
<td>15 (7)</td>
<td>0.0001</td>
</tr>
<tr>
<td>‘% maximal’</td>
<td>63 (14)</td>
<td>66 (17)</td>
<td>0.19</td>
</tr>
<tr>
<td>‘% possible’</td>
<td>34 (19)</td>
<td>44 (23)</td>
<td>0.004</td>
</tr>
<tr>
<td>‘% achievable’</td>
<td>64 (16)</td>
<td>72 (16)</td>
<td>0.0013</td>
</tr>
<tr>
<td>CV-PEFR (%)##</td>
<td>9 (5)</td>
<td>13 (6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PC\textsubscript{20} (mg hist /ml) ###</td>
<td>11.3</td>
<td>1.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

# Allergy was defined as at least one positive test out of seven RAST
## coefficient of variation of the weekly measured morning peak-flow during a four-week period at the start of the study
### geometric mean PC\textsubscript{20} values are given

Bronchodilator therapy
At the start of the study, all patients were randomly allocated to one of the two treatment regimens: continuous use of a bronchodilator (ipratropium bromide of 160 μg daily or salbutamol of 1,600 μg daily) or inhalation on demand. Within these treatment regimens, a cross-over comparison was applied between ipratropium bromide and salbutamol. All patients used ipratropium bromide during one year and salbutamol during the other. The sequence of salbutamol and ipratropium bromide was determined by random allocation. No corticosteroids, cromoglycate or bronchodilators other than the medication mentioned above (ipratropium bromide or salbutamol) were permitted.

Spirometry and bronchodilator testing
At the start of the study and after 6, 12, 13, 18 and 24 months, respectively, assessments were made by two trained laboratory technicians during an exacerbation-free
period. Patients were requested to abstain from bronchodilating medication for at least eight hours prior to the lung function tests. Smoking or exercise just before or during the experiments was not permitted. The FEV\textsubscript{1} and the forced vital capacity (FVC) were assessed three times by means of the Microspiro HI-298 (Chest Corporation, Japan) (20). The data from the flow-volume curve with the highest sum of FVC and FEV\textsubscript{1} were used for calculations. The FEV\textsubscript{1} was measured before and one hour after the inhalation of 400 μg salbutamol and 80 μg ipratropium bromide (both metered dose aerosol). The bronchodilating response of each patient on every test occasion was expressed in six different ways:

(1) Absolute change ('absolute') (4-6): \(\frac{\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}}}{\text{FEV}_{1\text{pre}}} \times 100\%\)

(2) Change as a percentage of prebronchodilator value ('% initial') (7,8):

\[\frac{\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}}}{\text{FEV}_{1\text{pre}}} \times 100\%\]

(3) Change as a percentage of predicted value ('% predicted') (5,9):

\[\frac{\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}}}{\text{FEV}_{1\text{pred}}} \times 100\%\]

(4) Change as a percentage of the maximal absolute response ever recorded during the two-year study period ('% maximal')(10):

\[\frac{\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}}}{\Delta \text{FEV}_{1\text{max}}} \times 100\%\]

(5) Change as a percentage of predicted value minus prebronchodilator value ('% possible') (12):

\[\frac{(\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}})}{(\text{FEV}_{1\text{pred}} - \text{FEV}_{1\text{pre}})} \times 100\%\]

(6) Change as a percentage of the highest postbronchodilator value ever recorded during the two-year study period minus prebronchodilator value ('% achievable')(10,11):

\[\frac{(\text{FEV}_{1\text{post}} - \text{FEV}_{1\text{pre}})}{(\text{FEV}_{1\text{max}} - \text{FEV}_{1\text{pre}})} \times 100\%\]

Analysis

Cross-sectional analysis. In order to investigate the dependence of the six indices for expressing reversibility of the prebronchodilator FEV\textsubscript{1}, linear regression analysis of the bronchodilating response (dependent variable) on the prebronchodilator FEV\textsubscript{1} (independent variable) was applied on six different test occasions. The Pearson correlation coefficient (r) was taken as a measure for the extent of the relationship (21).

Longitudinal analysis. The reproducibility of the bronchodilating response was determined by calculating the coefficient of variation (CV = SD/mean × 100\%) (22,23) of the six assessments. A low CV implies a high reproducibility and vice versa. The dependence of the six indices of the prebronchodilator FEV\textsubscript{1} was also
determined within-subjects. For this purpose, the six bronchodilating tests of an individual were incorporated in a linear regression analysis of the bronchodilating response (dependent variable) on the prebronchodilator lung function (independent variable). The r-square (% of explained variance) was taken as a measure for the extent of the relationship. Individual r-squares were averaged to get the mean r-square of that index in asthma or COPD. The mean CVs and mean r-square of the six indices were statistically compared with each other by ANOVA.

3.3. Results

Cross-sectional analysis
In Table 3.2 and Figure 3.1, the Pearson correlation coefficients of the relation between the bronchodilating response and the prebronchodilator FEV\textsubscript{1} at cross-sectional assessments are represented for six different indices of reversibility. The Pearson correlation coefficients of a particular index of reversibility varied substantially between the different cross-sectional assessments (Table 3.2). In asthma, the ‘absolute change’ and ‘% possible’ indices had no statistically significant correlations with the prebronchodilator FEV\textsubscript{1} at any test occasion. In COPD, only the ‘% possible’ and ‘% achievable’ indices had no significant correlations at any test moment. In both asthma and COPD, the average Pearson correlation coefficient was low (<0.20) for the ‘absolute change’, ‘% possible’ and ‘% achievable’ indices but high (≥0.45) for the ‘% initial’ index.

Table 3.2 Results of the cross-sectional analyses. The Pearson correlation coefficients of the relation between the bronchodilating response and the prebronchodilator FEV\textsubscript{1} are calculated at six different cross-sectional assessments for six indices of reversibility (between-subject analysis). The statistical significance of the correlations are also represented.

<table>
<thead>
<tr>
<th>Index</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>'Absolute'</td>
<td>-0.06</td>
<td>-0.07</td>
</tr>
<tr>
<td>' % Initial'</td>
<td>-0.39\dagger</td>
<td>-0.47\dagger</td>
</tr>
<tr>
<td>' % Predicted'</td>
<td>-0.24*</td>
<td>-0.26*</td>
</tr>
<tr>
<td>' % Maximal'</td>
<td>-0.28*</td>
<td>-0.22</td>
</tr>
<tr>
<td>' % Possible'</td>
<td>-0.22</td>
<td>-0.10</td>
</tr>
<tr>
<td>' % Achievable'</td>
<td>-0.16</td>
<td>+0.04</td>
</tr>
<tr>
<td></td>
<td>0.19*</td>
<td>-0.16</td>
</tr>
<tr>
<td>' % Initial'</td>
<td>-0.45\dagger</td>
<td>-0.48\dagger</td>
</tr>
<tr>
<td>' % Predicted'</td>
<td>-0.35\dagger</td>
<td>-0.35\dagger</td>
</tr>
<tr>
<td>' % Maximal'</td>
<td>-0.28***</td>
<td>-0.22*</td>
</tr>
<tr>
<td>' % Possible'</td>
<td>-0.09</td>
<td>+0.01</td>
</tr>
<tr>
<td>' % Achievable'</td>
<td>-0.13</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.005, \dagger p<0.001, † p<0.0001

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Figure 3.1 The correlation between response and prebronchodilator FEV₁ (cross-sectional analysis) of six different expression indices. The absolute Pearson correlation coefficients (mean of six different tests) are given in asthma (top) and COPD separately.
Longitudinal analysis
The results of the longitudinal analysis are shown in Table 3.3. All indices of reversibility demonstrated a pronounced relationship between the bronchodilating response and the prebronchodilator FEV₁, as represented by the high r-square. The reproducibility of the bronchodilating response was low: the CVs ranged from 34-50% in asthma to 46-61% in COPD. ‘% Possible’ and ‘% achievable’ appeared to be the indices with the lowest r-square and CV in both asthma and COPD.

Table 3.3 The results of the longitudinal analyses. The CVs of bronchodilating responses of six indices of reversibility. Moreover, the r-square (% of explained variance) of the relation between the bronchodilator response and the prebronchodilator lung function are also presented (within-subject analysis). The CVs and r-square of ‘% initial’ were statistically compared with the other indices by ANOVA.

<table>
<thead>
<tr>
<th>Index</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CV</td>
<td>r² x 100%</td>
</tr>
<tr>
<td>‘Absolute’</td>
<td>43 (24)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>‘% Initial’</td>
<td>50 (25)</td>
<td>63 (33)</td>
</tr>
<tr>
<td>‘% Predicted’</td>
<td>43 (24)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>‘% Maximal’</td>
<td>43 (24)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>‘% Possible’</td>
<td>34 (23)**</td>
<td>49 (34)*</td>
</tr>
<tr>
<td>‘% Achievable’</td>
<td>36 (21)**</td>
<td>40 (32)**</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.001, *** p<0.0001

The influence of the bronchodilator treatment regimen
During the two-year study period, there was a decline in the baseline FEV₁ of 85 (SEM 16) ml/yr during continuous bronchodilator treatment, but of only 39 (SEM 16) ml/yr during treatment on demand (unpaired Student’s t-test, p<0.05). The influence of the treatment regimen on the reproducibility of the bronchodilating response is given in Table 3.4 for the six different expression indices. It appeared that, in general, no differences existed in CV between continuous and on demand treated patients with asthma or COPD with one exception. In COPD, the CV of ‘% achiev-

Table 3.4 The influence of the treatment regimen during two years (continuous bronchodilator therapy versus treatment on demand) on the reproducibility of the bronchodilating response of six different expression indices. Differences in CV between continuous and on demand treatment group were tested by the unpaired Student’s t-test.

<table>
<thead>
<tr>
<th>Index</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Continuous</td>
<td>On demand</td>
</tr>
<tr>
<td>‘Absolute’</td>
<td>47 (22)</td>
<td>49 (25)</td>
</tr>
<tr>
<td>‘% Initial’</td>
<td>55 (22)</td>
<td>58 (30)</td>
</tr>
<tr>
<td>‘% Predicted’</td>
<td>47 (22)</td>
<td>49 (25)</td>
</tr>
<tr>
<td>‘% Maximal’</td>
<td>43 (24)</td>
<td>54 (34)</td>
</tr>
<tr>
<td>‘% Possible’</td>
<td>52 (55)</td>
<td>38 (29)</td>
</tr>
<tr>
<td>‘% Achievable’</td>
<td>41 (24)</td>
<td>39 (22)</td>
</tr>
</tbody>
</table>

* p<0.005

30
"able' was higher in patients treated on demand (62%) than in patients treated continuously (46%) (p<0.005).

3.4. Discussion

Nowadays, a number of indices to express the bronchodilating response are used, all of them with specific advantages and drawbacks. It is difficult to give general statements about the way bronchodilating responses should be expressed, because the method of expressing depends on the purpose of the bronchodilating test (1). Is the test used to separate asthmatics from subjects with COPD? Is it used to evaluate the bronchodilating efficacy of drugs or to predict the decline in lung function? It is not likely that only one index is most appropriate for answering all these different questions and indeed our study does not suggest 'one optimal index'.

Two general aspects of expressing the bronchodilating response were investigated in our study: the dependence on the prebronchodilator FEV₁ and the reproducibility of the bronchodilating response. In general, the use of an index independent from the prebronchodilator FEV₁ will increase the comparability of bronchodilating responses between different subjects and of repeated tests within the same subjects. Moreover, an index that gives more reproducible values will increase the validity of the test result. Therefore, an index least dependent on the prebronchodilator FEV₁ and with most reproducible values has many advantages.

Our study demonstrated that every index of expressing the bronchodilating response was to some extent dependent on the prebronchodilator FEV₁, in contrast to previous claims (13,16). However, some were clearly more dependent and, therefore less reproducible than others. The most common way to express the bronchodilating response ('% initial') was most dependent on the prebronchodilator FEV₁ and had the worst reproducibility. On the contrary, the '% possible' and '% achievable' indices were least dependent on the prebronchodilator FEV₁ and were most reproducible. This does not imply that bronchodilating responses should always be expressed as '% possible' or '% achievable'. For instance when the bronchodilating test is used to separate asthma from COPD, the data of our study and those of others (5) suggest that these indices might not give an optimal separation between the two disease categories and are, therefore, not appropriate for this purpose. In our study, the 'absolute', '% initial' and '% predicted' indices gave an optimal separation between asthmatics and subjects with COPD. Meslier et al. (6) and Eliasson et al. (5) found that the '% predicted' index was most useful in this respect.

When the bronchodilator test is used to evaluate the bronchodilating efficacy of a certain drug, the '% possible' or '% achievable' indices might be more useful than the other indices because of the higher reproducibility. Based on our results, the standard error of a single bronchodilator test can be estimated at 34-61%, dependent on the expression index. This indicates that at an individual level the value of a single bronchodilator test is limited. As the standard error generally decreases with the square root of the number of assessments (21), about 14 tests will bring the standard error of the mean within the 15% limit, when expressed as '% initial' in asthma. With
the '% possible' and '% achievable' indices, however, just seven assessments will give the same accuracy. Therefore, in bronchodilator trials, comparing the bronchodilating efficacy of different drugs within asthma or COPD, the '% possible' or '% achievable' indices might increase the possibility of detecting differences in bronchodilating efficacy between different drugs.

The index widely used is the one that expresses the absolute improvement in FEVi as a percentage of the prebronchodilator value. An advantage of this index is that it is easy to use and to calculate. A drawback is the strong dependence of the prebronchodilator FEVi. Small absolute changes become large percentage changes in patients with a low FEVi, so that these patients with the greatest impairment of lung function usually appear to have the greatest reversibility (5,13). In this study, the low reproducibility appeared to be another drawback of this index. Expressing the bronchodilating response as an absolute change is also very easy, but this index is dependent on sex and height: tall male patients are more likely to demonstrate a certain degree of reversibility than small female patients (6). Moreover, we found that the 'absolute change' index was also dependent of the prebronchodilator value, although to a smaller extent than the '% initial' index.

A recent cross-sectional study in non-asthmatic patients claimed that the '% predicted' index was the only index independent of the prebronchodilator FEVi (13). However, our study clearly demonstrated that this index is also dependent on the prebronchodilator FEVi, both between- and within-subjects. The Pearson correlations of the relation between bronchodilating response and the prebronchodilator lung function varied substantially between different cross-sectional assessments in our study. Therefore, only one cross-sectional measurement of the bronchodilating response as in the studies of Weir et al. (13) and Postma et al. (16) is not sufficient to compare different indices of reversibility.

The '% maximal' index (absolute change as a percentage of the maximal absolute response ever recorded) is not often used and appeared to have no specific advantages in this study. Data from our study showed that it is of no value in separating asthmatics from patients with COPD.

The '% possible' and '% achievable' indices are difficult to calculate, because predicted or maximal postbronchodilator values are necessary. In patients with little ventilatory impairment, bronchodilating responses expressed as '% possible' may be exaggerated because the prebronchodilator FEVi may reach the predicted value of the FEVi. The '% achievable' index does not have this drawback but repeated tests are necessary to determine the individual maximal postbronchodilator value. These limitations make this index useless in clinical practice.

The patients in this study were selected from 29 general practices and were representative for the adult population aged 30 and over with asthma or COPD (17,18). The FEVi varied widely between the patients in our study. It ranged from 50-130% at the start to 22-140% at the end of the two year study period.

In our study, high dosages of both an adrenergic and an anticholinergic agent were given. It is possible that the reproducibility of bronchodilating responses is worse when only one drug is given, when lower dosages are used, or when the bronchodilating responses are handled as a 'all-or-nothing' phenomenon (no response or a clear
response) (24). From the study of Lindgren et al. in five asthmatic patients, it could be inferred that the reproducibility of the bronchodilating response decreased (the CV increased by 6-22%), when instead of 2.25 mg, 0.25 mg terbutaline sulphate was administered (10).

The bronchodilator treatment regimen (continuous treatment or therapy on demand) appeared to have no influence on the reproducibility of the bronchodilating response. The only significant difference in CV between COPD patients treated continuously and those treated on demand (the CV of '% achievable') was probably an artifact. The reversibility at the start of the study appeared to be slightly higher in the on demand treated patients than in the COPD patients treated continuously. However, the baseline or prebronchodilator FEV$_1$ declined more rapidly during continuous bronchodilator treatment than during treatment on demand. This may have been the consequence of an increased exposure to allergens, cigarette smoke or other environmental triggers during continuous bronchodilator treatment (17,18). As a consequence of the decline in prebronchodilator lung function, the bronchodilating response increased in the course of time when expressed as ‘absolute’, ‘% initial’, ‘% predicted’ or ‘% maximal’, but it did not change when expressed as ‘% possible’ or ‘% achievable’. This might indicate that the ‘% possible’ or ‘% achievable’ indices are more useful in following the degree of reversibility in the course of time than the other indices.

The method in which bronchodilating responses should be expressed depends on the purpose of the test. From this study, it was concluded that the most common method of expressing bronchodilating responses (‘% initial’) appeared to be most dependent on the prebronchodilator FEV$_1$ and had the lowest reproducibility of the bronchodilating response. The ‘% possible’ (change as a percentage of the predicted minus the prebronchodilator value) and ‘% achievable’ (change as a percentage of the maximal postbronchodilator minus prebronchodilator value) indices were least dependent on the prebronchodilator FEV$_1$ and had the best reproducibility of the bronchodilating response. In bronchodilator studies, the latter expression indices increase the possibility of detecting differences in bronchodilating efficacy of different bronchodilator drugs.

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4. Early detection of patients with fast progressive asthma or chronic bronchitis in general practice*

Abstract
The morbidity and mortality due to asthma and chronic bronchitis are still rising in several countries. The aim of this study was to investigate whether early detection of patients with fast progressive asthma or chronic bronchitis in general practice was possible from a cross-sectional assessment of symptoms, smoking behaviour, quality of life, physical signs of the chest, allergy, and lung function. Data of 162 patients who had participated in a long term randomised controlled intervention study in general practice were analysed. 56 out of the 162 patients showed fast progressive disease (FPD, a rapid annual decline in the forced expiratory volume in one second (FEV₁) in combination with a high exacerbation rate). Measurements at the start of the study were used in a logistic regression analysis in order to detect the patients at risk (with FPD). A lower maximal expiratory flow at 50% of expired volume (MEF₅₀) was related to an increased risk of FPD in both asthma and chronic bronchitis (relative risks of 16.8 and 8.0 respectively, p<0.05). Most lung function indices, but also quality of life and pack years, were significant predictors of FPD in chronic bronchitis (p<0.05). However, it was not possible to detect FPD reliably with these predictors separately or even with the combination of several relevant clinical variables. 18% of the patients with chronic bronchitis and 22% of the patients with asthma were still misclassified.

It was concluded from this study that more than one measurement over time (monitoring) is necessary to detect the patients at risk. Monitoring should include assessments of objective ventilatory function indices (PEFR, FEV₁ or MEF₅₀).

4.1. Introduction

Both asthma and chronic bronchitis are considered to be progressive diseases in adulthood (1-3). Studies of the long-term course of asthma or chronic bronchitis showed that the annual decline in lung function was two to four times higher in patients than in random population samples (1-3). At an advanced stage of the disease, severe limitations in daily life may occur as a consequence of a low lung function level (4). In particular, patients with a rapid decline in lung function are at risk of disability or death at an early age due to chronic airflow obstruction. It has been hypothesized that adequate treatment at an early stage might prevent or decelerate deterioration in patients with airflow obstruction (5). Therefore, early detection and treatment of patients at risk (i.e. with a rapid decline in lung function) is important. As most patients with airflow obstruction are treated in primary health care, general practitioners in particular should be able to detect these patients at risk, preferably at an early stage. It is unclear how this can be carried out easily and effectively. In a randomised controlled intervention study in the Netherlands, the influence of bron-

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Cholinergic monotherapy on the progression rate was assessed in 162 patients with asthma or chronic bronchitis during two years (6,7). A subgroup of 56 patients showed fast progressive disease (rapid annual decline in lung function, high number of exacerbations per year). The present study investigated the possibility of predicting a fast progression rate at an early stage. Data from a single cross-sectional assessment of symptoms, smoking behaviour, quality of life, physical signs, allergy, and lung function indices at the start of the study were used for this purpose.

4.2. Methods

Patients
An extensive description was given previously of inclusion and exclusion criteria for patient selection (6,7). In summary: 29 general practitioners selected all their patients aged 30 and over with symptoms of asthma or chronic bronchitis. Only those patients who showed moderate airflow obstruction (FEV₁ or FEV₁/VC had to be two SD below their predicted value, but more than 50% of predicted value (8)) and/or bronchial hyperresponsiveness to histamine (PC₂₀ ≤ 8 mg/ml) were included. The criteria for diagnosis of asthma or chronic bronchitis were based on the standards of the American Thoracic Society (4,7). During the two-year study period, patients only received monotherapy with inhaled bronchodilators (salbutamol or ipratropium bro-

<table>
<thead>
<tr>
<th>Table 4.1 Characteristics at the start of the study of patients with FPD and SPD. SD in parenthesis. Differences between patients with SPD and FPD were tested by the chi-square test (dichotomous variables) or unpaired Student's t-test (continuous variables). 'FEV₁ decline' and 'exacerbations' were measured during the study.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td></td>
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<tr>
<td>Number</td>
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<tr>
<td>Age (years)</td>
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<td>Sex (M/F)</td>
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<tr>
<td>Pack years</td>
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<tr>
<td>Current smoker (+/-)</td>
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<tr>
<td>Symptom score</td>
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<tr>
<td>Quality of life</td>
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<tr>
<td>– pain score</td>
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<tr>
<td>– energy score</td>
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<tr>
<td>ALLERGY (++)</td>
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<tr>
<td>FEV₁ %pred</td>
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<tr>
<td>FEV₁/VC (%)</td>
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<tr>
<td>BDR-FEV₁ (%)</td>
</tr>
<tr>
<td>PC₂₀ (mg/ml) ##</td>
</tr>
<tr>
<td>FEV₁ decline (ml/yr)</td>
</tr>
<tr>
<td>Exacerbations (no./yr)</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.001
# Allergy was defined as at least one positive test out of seven RAST
## geometric mean PC₂₀ values are given
162 Patients participated during the two-year study period. No corticosteroids, theophyllines or cromoglycate were permitted. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent. The characteristics of patients with FPD and slowly progressive disease (SPD) are shown in Table 4.1.

**Initial assessments**

- **Questionnaire on respiratory symptoms, duration of the disease, smoking history and quality of life.** The severity of respiratory symptoms was assessed by means of the questionnaire of the Medical Research Council (Dutch version) in a score of 0-8 (6,7). The duration of the disease was defined as the current age minus age at which the first symptoms of asthma or chronic bronchitis appeared. The smoking history was assessed in pack years. Current smoking behaviour (smoker or non-smoker) was documented. The quality of life was assessed by using the Nottingham Health Profile (Dutch version, part one) (7). The items ‘energy score’ and ‘pain score’ (total range from 0-100%) were used in the analysis. A higher percentage corresponds with a lower experienced quality of life.

- **Lung function measurements.** All lung function measurements were carried out by two laboratory assistants. The bronchodilator medication was discontinued at least eight hours before the measurements. Firstly, static spirometric indices (FRC, IVC, RV, TLC) were assessed with the wet Gould® spirometer. Secondly, dynamic spirometry (FVC, FEV₁, PEFR, MEF₅₀, FIV₁) was carried out with the Microspiro HI-298® (Chest Corporation, Japan) (9). Thirdly, the bronchial (hyper)responsiveness to histamine was measured according to the method described by Cockcroft et al. and expressed as the provoking concentration of histamine in mg/ml producing a 20% fall in FEV₁ (PC₂₀-histamine values) (7). Finally, the bronchodilating response (BDR-FEV₁) was assessed 60 minutes after the inhalation of 400 μg salbutamol and 80 μg ipratropium bromide (metered dose aerosols). The response in FEV₁ was expressed as a percentage of the predicted or the prebronchodilator value.

- **Physical examination.** Physical examination of the chest (inspection, percussion and auscultation) was carried out by two trained medical doctors. Each of the following abnormal findings counted for one point in the physical sign score (maximum of 9 points): barrel-shaped chest, low-standing diaphragm, decreased diaphragmatic excursions, decreased expiratory breath sounds, prolonged expiratory phase, wheezing, noisy inspiratory sounds without auscultation, fine crackles and coarse crackles.

- **Allergy.** Patients were considered allergic if at least one of a 7-RAST tests was positive (RAST® test, Pharmacia, Sweden. Pollen: weeds, grasses, trees; Animals: cats and dogs; house dust mite; Aspergillus fumigates) (7).

**Follow-up measurements**

Assessments of the FEV₁ were repeated at six-month intervals during the two-year study period. Besides, the number of exacerbations during the two-year period were recorded by the general practitioner. Exacerbations were defined according to Fletcher et al. with small modifications of Boman et al. (10). 56 of the 162 patients
had fast progressive disease (FPD), which was defined as the combination of A. (lung function criteria) and B. (criteria for exacerbations):

A. an annual decline in FEV₁ of at least 80 ml/yr and/or irreversibility of airway obstruction to a bronchodilator (the increase in FEV₁, 60 minutes after maximal bronchodilatation with 80 μg ipratropium bromide and 400 μg salbutamol was smaller than 10% of the prebronchodilator value during at least one of the six test occasions during two years).

B. total number of exacerbations of at least one per year and/or total duration of exacerbations of at least three weeks per year.

All patients who did not meet the criteria for FPD had a slowly progressive disease (SPD).

**Analysis**

The annual decline in FEV₁ was estimated by linear regression of seven assessments during two years. Variables measured at the start of the study were used as predictors of FPD in a logistic regression analysis (11). For this purpose, all parameters were dichotomised (≤ mean value / > mean). The relative risks, the 95% confidence limits and the statistical significance were calculated for all predictors separately (univariate analysis) and for a combination of clinically relevant predictors (multivariate analysis). Receiver-operating characteristic (ROC) curves were calculated for the multivariate models in asthma and chronic bronchitis by plotting sensitivity (vertical axis) against 1-specificity (horizontal axis)(11). The area under the ROC-curve (AUC) is a measure for the predictive value; it is optimal when AUC is 0.95-1.00, minimal when AUC is near 0.50 (11). The AUC represents the probability of ranking patients correctly as having FPD or SPD.

**4.3. Results**

The relative risks (95% confidence limits in brackets) and the statistical significance of all separate predictors are presented in Table 4.2. In asthma, the MEF₅₀ was the only statistically significant predictor of FPD (p<0.05). The risk of FPD in patients with a MEF₅₀ below 1.7 l/s was almost four times as high as in patients with a MEF₅₀ above 1.7 l/s. In chronic bronchitis patients, a higher number of pack years and a lower reported quality of life (energy score) were associated with an increased risk of FPD. Moreover, a lower ventilatory function (PEFR, FEV₁, MEF₅₀) a higher FRC/TLC and a lower degree of bronchial responsiveness to histamine (PC₂₀) were related to an increased risk of FPD in chronic bronchitis. In both asthmatic and chronic bronchitis patients, the MEF₅₀ was the strongest predictor (relative risk of 3.9 and 4.5 respectively).

The results of the multivariate analysis are shown in Table 4.3. In asthmatic patients, the duration of the disease was also a significant predictor of FPD after adjusting for the MEF₅₀. No other variables at the start of the study in asthma were statistically significant predictors of FPD. In chronic bronchitis patients, age, pack years and the MEF₅₀ were independent predictors of FPD (p<0.05). By means of a step-
**Table 4.2** The predictive value of all predictors separately (univariate logistic regression analysis). Relative risks (95% confidence limits in brackets) and the statistical significance are shown.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative risk</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
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<td></td>
</tr>
<tr>
<td>Age (≤49 yrs/&gt;49)</td>
<td>1.42</td>
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</tr>
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<td>Sex (M/F)</td>
<td>0.80</td>
<td>0.66</td>
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<tr>
<td>Height (≤1.7m/&gt;1.7)</td>
<td>0.98</td>
<td>0.97</td>
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<tr>
<td>Pack years (≤12/&gt;12)</td>
<td>0.75</td>
<td>0.58</td>
</tr>
<tr>
<td>Current smoking (+/-)</td>
<td>0.92</td>
<td>0.88</td>
</tr>
<tr>
<td>Duration of disease (≤22 yrs/&gt;22)</td>
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<td>0.26</td>
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<tr>
<td>Symptom score (≤5/&gt;5)</td>
<td>0.67</td>
<td>0.44</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– energy score (≤29/&gt;29)</td>
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<td>0.92</td>
</tr>
<tr>
<td>– pain score (≤9/&gt;9)</td>
<td>0.99</td>
<td>0.98</td>
</tr>
<tr>
<td>Physical sign score (≤1.3/&gt;1.3)</td>
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<td>0.46</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
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<td>0.43</td>
</tr>
<tr>
<td>FEV₁ (≤73% pred/&gt;73)</td>
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<tr>
<td>BDR-FEV₁ (≤16%/&gt;16)</td>
<td>1.14</td>
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</tr>
<tr>
<td>PEFR (≤51 s⁻¹/&gt;51)</td>
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<td>0.58</td>
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<tr>
<td>MEF₅₀ (≤1.7 l s⁻¹/&gt;1.7)</td>
<td>3.90</td>
<td>0.02</td>
</tr>
<tr>
<td>PC₂₀ (≤3.2 mg m⁻¹/&gt;3.2)</td>
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<td>TLC (≤6 l/&gt;6)</td>
<td>0.94</td>
<td>0.91</td>
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<td>FIV₁/IVC (≤83%/&gt;83)</td>
<td>1.36</td>
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<td>FRC/TLC (≤54%/&gt;54)</td>
<td>0.82</td>
<td>0.69</td>
</tr>
<tr>
<td>Helium slope (≤3% s⁻¹/&gt;3)</td>
<td>0.67</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Chronic bronchitis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age (≤52 yrs/&gt;52)</td>
<td>1.25</td>
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<td>Sex (M/F)</td>
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<td>Height (≤1.7m/&gt;1.7)</td>
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<tr>
<td>Pack years (≤18/&gt;18)</td>
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<td>0.02</td>
</tr>
<tr>
<td>Current smoking (+/-)</td>
<td>1.70</td>
<td>0.24</td>
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<tr>
<td>Duration of disease (≤20 yrs/&gt;20)</td>
<td>0.64</td>
<td>0.32</td>
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<td>Symptom score (≤5/&gt;5)</td>
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<tr>
<td>Quality of life</td>
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<td></td>
</tr>
<tr>
<td>– energy score (≤22/&gt;22)</td>
<td>0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>– pain score (≤13/&gt;13)</td>
<td>0.64</td>
<td>0.36</td>
</tr>
<tr>
<td>Physical sign score (≤1.3/&gt;1.3)</td>
<td>0.47</td>
<td>0.10</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
<td>0.64</td>
<td>0.36</td>
</tr>
<tr>
<td>FEV₁ (≤78% pred/&gt;78)</td>
<td>4.44</td>
<td>0.004</td>
</tr>
<tr>
<td>BDR-FEV₁ (≤8%/&gt;8)</td>
<td>0.66</td>
<td>0.35</td>
</tr>
<tr>
<td>PEFR (≤6 l s⁻¹/&gt;6)</td>
<td>2.92</td>
<td>0.03</td>
</tr>
<tr>
<td>MEF₅₀ (≤2.1 l s⁻¹/&gt;2.1)</td>
<td>4.48</td>
<td>0.006</td>
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<td>PC₂₀ (≤16 mg m⁻¹/&gt;16)</td>
<td>2.80</td>
<td>0.03</td>
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<tr>
<td>TLC (≤6 l/&gt;6)</td>
<td>1.53</td>
<td>0.34</td>
</tr>
<tr>
<td>FIV₁/IVC (≤86%/&gt;86)</td>
<td>0.70</td>
<td>0.44</td>
</tr>
<tr>
<td>FRC/TLC (≤52%/&gt;52)</td>
<td>0.31</td>
<td>0.01</td>
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<tr>
<td>Helium slope (≤3% s⁻¹/&gt;3)</td>
<td>0.41</td>
<td>0.06</td>
</tr>
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</table>


Table 4.3 The predictive value of the combination of several clinically relevant predictors (multivariate logistic regression analysis). Relative risks (95% confidence limits in brackets) and the statistical significance are shown.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative risk</th>
<th>p-value</th>
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<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (≤49 yrs/&gt;49)</td>
<td>1.04</td>
<td>0.41</td>
</tr>
<tr>
<td>Pack years (≤12/&gt;12)</td>
<td>1.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Current smoking (+/-)</td>
<td>0.75</td>
<td>0.73</td>
</tr>
<tr>
<td>Duration of disease (≤22 yrs/&gt;22)</td>
<td>5.25</td>
<td>0.026</td>
</tr>
<tr>
<td>Symptom score (≤5/&gt;5)</td>
<td>0.33</td>
<td>0.14</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– energy score (≤29/&gt;29)</td>
<td>2.16</td>
<td>0.39</td>
</tr>
<tr>
<td>– pain score (≤9/&gt;9)</td>
<td>1.16</td>
<td>0.87</td>
</tr>
<tr>
<td>Physical sign score (≤1 3/&gt;1 3)</td>
<td>0.74</td>
<td>0.70</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
<td>1.94</td>
<td>0.45</td>
</tr>
<tr>
<td>BDR-FEV1 (≤16%/&gt;16)</td>
<td>1.83</td>
<td>0.40</td>
</tr>
<tr>
<td>MEF50 (≤1 7 l s⁻¹/&gt;1 7)</td>
<td>16.8</td>
<td>0.003</td>
</tr>
<tr>
<td>PC20 (≤3 2 mg ml⁻¹/&gt;3 2)</td>
<td>1.19</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Chronic bronchitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (≤52 yrs/&gt;52)</td>
<td>1.07</td>
<td>0.026</td>
</tr>
<tr>
<td>Pack years (≤18/&gt;18)</td>
<td>0.19</td>
<td>0.020</td>
</tr>
<tr>
<td>Current smoking (+/-)</td>
<td>1.27</td>
<td>0.67</td>
</tr>
<tr>
<td>Duration of disease (≤20 yrs/&gt;20)</td>
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<td>0.48</td>
</tr>
<tr>
<td>Symptom score (≤5/&gt;5)</td>
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<td>0.42</td>
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<tr>
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<td>0.08</td>
</tr>
<tr>
<td>– pain score (≤13/&gt;13)</td>
<td>0.40</td>
<td>0.22</td>
</tr>
<tr>
<td>Physical sign score (≤1 3/&gt;1 3)</td>
<td>0.71</td>
<td>0.58</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
<td>0.66</td>
<td>0.64</td>
</tr>
<tr>
<td>BDR-FEV1 (≤8%/&gt;8)</td>
<td>1.02</td>
<td>0.98</td>
</tr>
<tr>
<td>MEF50 (≤2 1 l s⁻¹/&gt;2 1)</td>
<td>7.98</td>
<td>0.007</td>
</tr>
<tr>
<td>PC20 (≤16 mg ml⁻¹/&gt;16)</td>
<td>1.31</td>
<td>0.66</td>
</tr>
</tbody>
</table>

wise forward procedure, it was investigated whether the remaining variables, which were not included in the multivariate model added significantly to the predictive value of the multivariate model. It appeared that in asthmatic patients no variables entered the model. In chronic bronchitis patients, only the FIVI/IVC was added to the other variables already in the model (Relative risk=0.25 (95% confidence limits 0.07-0.92), p=0.033).

The ROC-curves of the multivariate models in asthma and chronic bronchitis are shown in Figures 4.1 and 4.2, respectively. The AUC was 0.78 in asthma and 0.82 in chronic bronchitis. This implies that (100-78)%=22% of the patients with asthma and (100-82)%=18% of the patients with chronic bronchitis are misclassified in the FPD or the SPD category. Adding the FIVI/IVC to the multivariate model in chronic bronchitis did not significantly enlarge the AUC (AUC was 0.85, p=0.28).
4.4. Discussion

Morbidity and mortality due to asthma and chronic bronchitis are still rising in several countries (12,13). Underdiagnosis and undertreatment of asthma and chronic bronchitis have been reported in general practice (6,14). Various factors at both patient and doctor level may be responsible for this situation (14,15). Moreover, there are indications that certain bronchopulmonary drugs may be involved in the increase of morbidity and mortality (7,16). Continuous monotherapy with bronchodilators, though effective in relieving symptoms, appeared to have an accelerating influence on the long-term progression of asthma and chronic bronchitis (7). The current understanding that inflammation plays a major role in the pathophysiology of airway obstruction led to a shift in treatment policy towards the early introduction of inhaled steroids (17). This study deals with the early detection in general practice of patients at risk, i.e. with a high annual decline in ventilatory function and a high number of exacerbations per year. These patients with FPD are at risk of disability or death due to chronic airway obstruction at an early age. There is evidence that early detection
The Receiver-Operating Characteristic (ROC) curve of the combination of clinically relevant predictors in chronic bronchitis.

* The curves of a model with the FIV1/IVC (———) and without this parameter (———) are shown.

of these patients is useful. A trial with an inhaled corticosteroid (beclomethasone dipropionate of 800 μg daily) during one year after the present study demonstrated that FPD was decelerated, particularly in asthma (18). From the present study, it appeared that one cross-sectional assessment of several clinically relevant variables was not enough to detect all patients at risk already at an early stage. 18-22% of the patients were still misclassified. Burrows et al. investigated the predictive value of screening spirometry for the annual decline in FEV₁ in a sample from the general population (19). They also observed that one assessment of spirometry was not enough to detect all patients at risk, particularly in women. More measurements in time would probably make the detection more reliable, i.e. monitoring of patients with asthma and chronic bronchitis. A fast progression in the patients of this study was not accompanied by a worsening of symptoms. This may indicate that (change of) symptoms poorly reflect(s) the severity and progression of airway obstruction. Therefore, measurements of ventilatory function are essential in following the course of asthma and chronic bronchitis (19) and will greatly improve the quality of care in chronic respiratory disorders.
The patients in our study were not a selected group of patients but were representative of the adult patient population (30 years and over) with asthma and chronic bronchitis in 29 general practices (6,7). It may be argued that the definition of FPD in this study was rather subjective. However, we also carried out multiple linear regression, using the annual decline in FEV₁, the number and duration of exacerbations as separate dependent variables. Almost the same variables as in the logistic regression analysis appeared to be of significance. The annual decline in FEV₁ is the most important measure for progression in studies on this subject (1-3). The number of exacerbations per year is an important measure for the clinical severity of the disease (10) and it was also related to the annual decline in lung function (3). To be sure about the progressive nature of the disease, FPD was defined in terms of both lung function decline (physiological parameter) and exacerbation rate (clinical parameter).

In our study, several factors in asthma and chronic bronchitis were related to an increased risk of FPD. In asthma, a shorter duration of the disease (current age minus the age at which the first symptoms occurred) was related to a higher occurrence of FPD. Although asthma is often looked upon as a disease of the young, it is possible that symptoms of asthma do not manifest themselves before the age of 40 or 50 (4). This late-onset type of asthma may have a more progressive character. It is probably this type of asthma that explained our finding that a shorter duration of the disease was a risk factor for FPD. In chronic bronchitis, a higher number of pack years (>18) was a risk factor for FPD. This is not strange in a disease in which smoking is thought to be the main aetiologic factor (4). This finding once again stressed the importance of quitting or reducing smoking. The general practitioner plays a crucial role in achieving this difficult goal. In both asthma and chronic bronchitis, a lower ventilatory function was accompanied by an increased occurrence of FPD. This suggested that airway obstruction itself is a risk factor for a more rapid progression of disease. This phenomenon was previously described by Burrows et al. as the 'horse-racing effect' (19).

It was concluded that the early detection of patients who run the risk of developing fast progressive asthma or chronic bronchitis was hardly possible on the basis of one cross-sectional assessment of clinically relevant variables. Repeated measurements (monitoring of patients) are necessary to make the detection more reliable. Monitoring patients with airway obstruction also implies assessments of ventilatory function.

References


5. Does bronchial hyperresponsiveness precede or follow airway obstruction in asthma or COPD?*

Abstract
The following hypothesis was tested. The degree of bronchial hyperresponsiveness (BHR) is a risk factor for the progression of airway obstruction in asthma, while in COPD it reflects the existing airway obstruction. The relationships between the (annual change in) PC20-histamine and the (annual change in) FEV1 were investigated in a two-year prospective controlled study. The FEV1 and the PC20-histamine were assessed at six-month intervals. 183 Patients (74 asthma, 109 COPD) participated. The investigated relationships were assessed by means of multiple analysis of variance (MANOVA). Patients used bronchodilator therapy alone. No steroids were permitted during the study.

The results demonstrated that the PC20 at the start of the study was related to the subsequent annual decline of FEV1 in asthma (r=0.32, p<0.05) but not in COPD (r=-0.10, p=0.885). Asthmatic patients with a PC20-value ≤2 mg/ml had an average decline of -118 ml/yr, those with a PC20-value >2 mg/ml of -27 ml/yr. The change of PC20-histamine during the two-year study period was related to the annual change of FEV1 in COPD (r=0.45, p<0.05), but not in asthma (r=0.06, p=0.898). The disturbing influence of possible confounders was investigated and if necessary controlled for (age, sex, height, past and current smoking, allergy, FEV1, bronchodilator response, PC20, exacerbations and the bronchodilator treatment during the study).

It was concluded that BHR, assessed with the PC20-histamine, is involved in the progression of airway obstruction in asthma. In COPD, however, the degree of BHR probably only reflects the degree of existing airway obstruction.

5.1. Introduction
Nonspecific hyperresponsiveness of the bronchi (BHR) is regarded as a hallmark of asthma (1,2) and is often present in Chronic Obstructive Pulmonary Disease (COPD) (3). The degree of BHR correlates with the severity of the disease in terms of treatment requirement in asthma (2,4) and of ventilatory function impairment in both asthma (5,6) and COPD (7). An important question is whether BHR is a risk factor for the progression of airway obstruction in asthma and COPD (8). In several studies, a relationship was found between BHR and the annual decline in ventilatory function (9-13). In many of these studies, however, BHR was assessed at the end of the study period. Therefore, it was not clear whether BHR preceded or followed the loss in lung function (8). BHR may be a risk factor for the decline in lung function. Particularly in asthma, BHR is related to inflammation of the airways. Release of eosinophilic proteins, oxygen radicals and proteolytic enzymes from various inflammatory cells may damage the epithelium and may increase BHR (14,15). Chronic inflammato-

*Submitted for publication as Dompe"ling E, Van Schayck CP, Molema J, Folgering H, Van Grunsven PM, Van Weel C. Does bronchial hyperresponsiveness precede or follow airway obstruction in asthma or COPD?
tion may lead to structural changes such as hypertrophy of airway smooth muscle and thickening of the basement membrane (14,15) which may result in loss of lung function. On the other hand, the measurements of BHR may reflect the already existing airway obstruction. Particularly in COPD, the response to bronchodilator and bronchoconstrictor stimuli is known to be determined to a large extent by the geometry of the airways (8,16-17). It has been suggested that the role of BHR in the progression of asthma and COPD may be different (8,18); BHR may be a risk factor for the progression of airway obstruction in asthma but not in COPD.

The aim of this study was to test the hypothesis that BHR is a risk factor for progression of airway obstruction in asthma, while in COPD it only reflects the degree of existing airway obstruction. During two years, a prospective controlled study was carried out with 74 asthmatic patients and 109 patients with COPD.

5.2. Methods

Patients
An extensive description of patient selection, in- and exclusion criteria of the two-year study has been given before (19-21). In summary: 29 general practitioners were asked to select all their patients aged 30 and over with symptoms of asthma or COPD. Only those patients who showed moderate airway obstruction (FEV1 or FEV1/EVC had to be two standard deviations below their predicted value but higher than 50% of the predicted value) and/or bronchial hyperresponsiveness to histamine (PC20 ≤8 mg/ml) were included by the investigators. The predicted values were based on the equations of the European Coal and Steel Community (22). Exclusion criteria were: dependence on corticosteroids, chronic heart failure, malignant disorders or other severe, life-threatening diseases. A study of random samples of patients who refused to participate or who were excluded by their general practitioner for reasons other than their pulmonary disease revealed no differences in clinical characteristics between the patients in the study and the excluded subjects (19). Therefore, no recruitment bias had been introduced in the selection procedure. The criteria for diagnosis of asthma and COPD was based on the standards of the American Thoracic Society (ATS) (1). Asthma was defined as the combination of (20,21): 1. Bronchial hyperresponsiveness to histamine (PC20 ≤8 mg/ml); 2. Reversible obstruction (FEV1 improved more than 15% of the prebronchodilator value, 60 minutes after the administration of 80 μg ipratropium bromide and 400 μg salbutamol); 3. Dyspnœa; 4. Allergy and/or wheezing.

COPD was defined as the combination of (20,21): 1. Chronic cough or chronic sputum production in at least three months during at least two consecutive years; 2. Continuous airway obstruction (FEV1 ≤85% of the predicted value).

Although separate features of asthma and COPD were not mutually exclusive (i.e. some patients with COPD had PC20-values ≤8 mg/ml, some asthmatic patients suffered from chronic cough), the combination of features was: no patients with asthma also had COPD and vice versa. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.
Treatment
Patients were either treated continuously (salbutamol 400 μg or ipratropium bromide 40 μg, four times daily) or 'on demand' (only dry powder inhalations of salbutamol or ipratropium bromide during periods of dyspnoea or exacerbations). Patients using ipratropium bromide during the first year crossed-over to salbutamol during the second and vice versa. The treatment regimen (continuous or on demand) and the order of the drugs was determined by random allocation. In an eight-week wash-out period before the start of the study, bronchopulmonary medication other than the study medication was stopped (corticosteroids, sodium cromoglycate, theophylline, etc).

Measurements
Spirometry was carried out at the start of the study and after 1, 6, 12, 13, 18 and 24 months (7 measurements) with the Microspiro HI-298® (Chest Corporation, Japan) (23). Bronchodilator medication was discontinued at least eight hours before the spirometric tests. On all occasions, each patient had to perform three satisfactory forced vital capacity (FVC) manoeuvres. Data were taken from the curve with the highest sum of FVC and FEV1. The bronchodilating response was measured by the relative increase in FEV1 compared to the predicted value, 60 minutes after the inhalation of 400 μg salbutamol and 80 μg ipratropium bromide (both metered dose aerosols). Spirometric assessments and measurements of the PC20-histamine were carried out in stable periods of the disease, at least six weeks after an exacerbation.

BHR to histamine was assessed according to the method described by Cockcroft et al. (2) at the start, and after 6, 12, 18 and 24 months. Subjects first performed spirometry correctly three times on the Microspiro HI-298®. An aerosol of buffered saline was then inhaled, followed by aerosols of histamine acid phosphate in doubling concentrations from 0.03 to 32 mg/ml at five minute intervals. Spirometry was repeated once after 30, and after 90 seconds following each inhalation. The inhalations of histamine were discontinued when there was a fall in FEV1 of 20% of the value before saline inhalation or when 32 mg/ml of histamine had been administered. The 20% fall had to be found during either the 30 or the 90 second test after each dose. The histamine provocation test was not performed when the FEV1 was below 50% of the predicted value.

At the start of the study, presence of allergy (7-RAST tests, Pharmacia, Sweden. Pollen: weeds, grasses, trees; animals: cats and dogs; house dust mite; Aspergillus Fumigatus) was assessed. Patients were considered allergic if at least one of the seven tests was positive. Smoking history was retrospectively assessed in pack years. During the study, the number of exacerbations was recorded by the general practitioner. Current smoking habits (number of cigarettes smoked per day) were recorded by the patients in a weekly diary.

Analysis
Multiple analysis of variance (MANOVA) was applied to assess the following relationships:
1. between the PC20 and the FEV1 at the start of the study (cross-sectional assessments);
2. between the PC$_{20}$ at the start of the study and the subsequent annual decline in FEV$_1$; the annual decline in FEV$_1$ was estimated by linear regression of FEV$_1$ in the course of time. The PC$_{20}$ was handled continuously ($^{10}\log$ normal) and dichotomously ($\leq$ mean / $>$ mean).

3. between the annual change of PC$_{20}$ and the annual decline in FEV$_1$ during the study. The annual change of PC$_{20}$ was estimated by linear regression of $^{10}\log$ PC$_{20}$ in the course of time.

A possibly confounding influence of the following covariates on the above mentioned relationships was investigated: age, sex, height, allergy, pack years, smoking, number of exacerbations per year, bronchodilating response, treatment regimen during the study and (dependent on the investigated relationship) initial FEV$_1$ and PC$_{20}$ ($^{10}\log$ transformed). When a covariate was to some extent related to the dependent variable ($p<0.10$) it remained in the multivariate model in order to correct for a possibly confounding influence.

Two-sided $p$-values $<0.05$ were considered statistically significant.

5.3. Results

Clinical characteristics

At the start of the study, patients with asthma were characterized by a lower number of smokers, less pack years, more allergic patients, a higher reversibility of obstruction and a severer bronchial hyperresponsiveness than patients with COPD (Table 5.1).

Table 5.1 Clinical characteristics of patients with asthma and COPD in this study. The differences between asthma and COPD were tested by means of the unpaired Student's $t$-test (normally distributed variables) or by the chi-square test (class variables). Standard deviations are given in parentheses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>74</td>
<td>109</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 (13)</td>
<td>53 (13)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>34/40</td>
<td>66/43</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- current</td>
<td>29</td>
<td>65</td>
</tr>
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<td>- ex</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>- never</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Pack years</td>
<td>13 (16)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>25/48</td>
<td>16/91</td>
</tr>
<tr>
<td>FEV$_1$ (% pred)</td>
<td>73 (21)</td>
<td>78 (17)</td>
</tr>
<tr>
<td>Bronchodilating response (%)</td>
<td>15 (10)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>PC$_{20}$ (mg/ml)##</td>
<td>2.4</td>
<td>14.0</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.01, ***p<0.005, ****p<0.0001
# Allergy was defined as at least one positive test out of seven RAST
## geometric mean PC$_{20}$-values are given
Cross-sectional assessments

At the start of the study, a significant relationship existed between the PC20 and FEV1 (cross-sectional assessment). However, the relationship was stronger in COPD (r=0.71, p<0.0001) than in asthma (r=0.51, p<0.01).

The relationship between the initial PC20 and the subsequent annual decline in FEV1

When the PC20 at the start of the study was related to the subsequent annual decline in FEV1, a significant relationship was found in asthma (r=0.32, p<0.05) but not in COPD (r=-0.10, p=0.885). In asthma, the annual decline in FEV1 in patients with a PC20 ≤2 mg/ml was -118 ml/yr but only -27 ml/yr in those with a PC20 >2 mg/ml (Table 5.2). In patients with COPD, the annual decline in FEV1 of -83 ml/yr in patients with a PC20 ≤8 mg/ml was not different from the decline of -90 ml/yr in those with a PC20 >8 mg/ml (Table 5.2).

Table 5.2 The annual decline in FEV1 in patients, dichotomized according to their PC20 at the start of the study (≤ rounded mean / > rounded mean). The annual decline in FEV1 between the two PC20-classes was statistically compared by the unpaired Student's t-test. Standard error of the mean between parenthesis.

<table>
<thead>
<tr>
<th>Asthma</th>
<th>PC20-histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 2 mg/ml</td>
</tr>
<tr>
<td>Change in FEV1 (ml/yr)</td>
<td>-27 (51) (n=29)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COPD</th>
<th>PC20-histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 8 mg/ml</td>
</tr>
<tr>
<td>Change in FEV1 (ml/yr)</td>
<td>-90 (31) (n=71)</td>
</tr>
</tbody>
</table>

The relationship between the annual change in PC20 and the annual decline in FEV1

Only in patients with COPD was the annual change of the PC20 significantly related to the annual decline of FEV1 (r=0.47, p=0.048) (Figures 5.1 and 5.2). In asthma, no relationship was found (r=0.06, p=0.898).

Confounding factors

The bronchodilating response (reversibility of obstruction) at the start of the study was to some extent related to the decline in FEV1 in both asthma (estimate +3.1(SEM 1.6) ml/yr, p=0.061) and COPD (estimate +3.2(1.8), p=0.069). No other covariates (e.g. the FEV1 at the start of the study or allergy) were related to the annual decline in FEV1. Smoking was not a confounder in COPD as neither in the group as a whole
nor in the current smokers, the PC<sub>20</sub> was related to the annual decline in FEV<sub>1</sub> (p=0.885 and p=0.825 respectively).

In asthma, the annual change in PC<sub>20</sub> was only related to smoking (estimate +0.80(SEM 0.33) doubling dose/yr, p=0.020). In COPD, the annual deterioration in PC<sub>20</sub> was larger in patients with a higher number of exacerbations per year (estimate −0.37(SEM 0.10), p=0.0009). In MANOVA, the investigated relationships were adjusted for these possible confounders.

5.4. Discussion

The present longitudinal study demonstrated an important difference in BHR between asthmatics and patients with COPD. The PC<sub>20</sub>-histamine at the start of the two-year study was related to the subsequent annual decline in FEV<sub>1</sub> in asthma but
Figure 5.2 The relation between the annual change of the PC$_{20}$ and the annual decline of FEV$_1$ in COPD. *

![Graph showing the relation between annual change of PC$_{20}$ and annual decline of FEV$_1$.](image)

* change PC$_{20} = -0.047 + 0.00048$ change FEV$_1$ (r=0.45, p=0.022)

not in COPD. Moreover, changes in PC$_{20}$ during two years were closely related to the changes in FEV$_1$ in COPD but not in asthma. These findings supported the hypothesis that the degree of bronchial hyperresponsiveness (BHR) is a risk factor for the progression of airway obstruction in asthma, while in COPD it reflects the existing airway obstruction. It might indicate that BHR is a 'cause' of airflow obstruction in asthma whereas it is a 'consequence' of airflow obstruction in patients with COPD (8). It also suggests distinctive mechanisms of BHR in asthma and COPD (18).

There is currently a lot of interest in the similarities and discrepancies in BHR between asthma and COPD (24). In both asthma and COPD, an increased response to histamine or methacholine might be present (1), although BHR is more characteristic for asthma than for patients with COPD. Asthmatics and patients with COPD differ in the shape of the dose-response curve to histamine or methacholine (25). In asthma, both a leftward shift of the dose-response curve ('hypersensitivity') and a lift of the maximal response plateau (increase in maximal degree of airway narrowing) occur
(26), while in COPD, BHR is often only characterized by hypersensitivity (27). A leftward shift might be regarded as being the results of any augmentation of the airway narrowing stimuli ('prejunctional mechanism'), elevation of the maximal response plateau the result of any increase in the response to the effector organ ('post-junctional mechanism') (25,28). The results of the present study might fit these different mechanisms in asthma and COPD.

In the COPD patients of this study, the PC$_{20}$ was largely determined by the geometry of the airways. Indeed, a decreased airway calibre may be one of the mechanisms of BHR (29). As resistance in the airways is inversely proportional to the fourth power of the radius, a constriction of a narrow airway causes a much greater change in airway resistance than the same constriction of a more dilated airway (29,30). Therefore, patients with a more severe airway obstruction are more likely to respond to a certain concentration of histamine with a 20% fall in FEV$_1$ than others with a less severe obstruction. This might emphasize the role of prejunctional factors as the mechanism for BHR in COPD. In asthma, the degree of BHR is known to be related to the severity of the inflammatory processes underlying the disease. Release of eosinophilic proteins, oxygen radicals and proteolytic enzymes from various inflammatory cells may damage the epithelium and may increase BHR (14,15). Chronic inflammation may lead to structural changes such as hypertrophy of airway smooth muscle and thickening of the basement membrane (14,15) which may result in loss of lung function. This concept might be an explanation for BHR as a risk factor for decline in lung function and for the pre- and postjunctional mechanisms of BHR in asthma.

The data of the present study suggested that assessments of the PC$_{20}$ in asthma might indicate the risk on a rapid progression of airway obstruction. Patients with a PC$_{20} \leq$2 mg/ml demonstrated an average 99 ml/year faster decline in FEV$_1$ than subjects with a PC$_{20} >$2 mg/ml. The decline in FEV$_1$ of 118 ml/yr in the subjects with marked BHR was surprisingly high and may also reflect the failure of bronchodilator therapy in addressing the inflammatory processes in the airways of these patients (20,31). Therefore, asthmatic subjects with marked BHR run the risk of developing a progressive decline in lung function. In an early stage, these patients may be treated with drugs which are known to decrease BHR by modulating inflammatory processes, inhaled corticosteroids, nedocromil or cromolyn sodium. A trial with inhaled corticosteroids after the present study demonstrated that the loss of lung function during bronchodilators alone was reversed by inhaled corticosteroids, particularly in asthma (32).

The results of the present study were based on multiple assessments of the PC$_{20}$-histamine and the FEV$_1$ in a controlled prospective study during two years. The influence of possible confounders such as initial FEV$_1$ level, degree of bronchodilating response, past and current smoking on the investigated relationships was assessed and if necessary controlled for. During the two-year study period, patients used the study medication of the bronchodilator intervention study and were not permitted to use sodium cromoglycate or corticosteroids. The patients' PC$_{20}$ and FEV$_1$ were measured during stable periods of the disease, at least six weeks after an exacerbation. The discriminating capacity in the analysis of decline in FEV$_1$ was high be-
cause (20): a) a relatively large number of subjects participated; b) seven measure-
ments of the FEVi were used; c) the data of the FEVi fitted clearly in a linear model.
On account of the high discriminating capacity, a study period of two years was suffi-
cient to demonstrate relationships between the annual changes in lung function and
the (annual changes in) BHR.

Definition criteria of asthma and COPD were not a confounder in this study. In
COPD, 30% of the patients had a PC20 ≤8 mg/ml. The presence of a PC20 ≤8 mg/ml
was only one of the diagnostic criteria for asthma and did not exclude a diagnosis of
COPD. The patients in this study were representative of the patient population with
asthma or COPD and mild to moderate airway obstruction (FEVi ≥ 50% of the pre-
dicted value) (19).

As far as we know there are no other controlled prospective studies on both as-
thma and COPD in which it was investigated whether BHR preceded or followed the
progression of airway obstruction. However, one study on asthma (10) and some
studies on chronic airway obstruction (9,11-13) investigated the relation between the
BHR and the annual decline in ventilatory function. A drawback of many of these
studies is that the BHR was assessed at the end of the study period. It this case it is
not clear whether BHR was the 'cause' or the 'consequence' of the decline in lung
function (8). In the study of Postma et al., 81 non-allergic patients with chronic air-
way obstruction were studied (11). The nonspecific bronchial hyperresponsiveness,
measured at the start of the study, was related to an increased decline in FEVi in the
smokers, but not in the ex-smokers. All their patients received regular bronchodilator
therapy and had a more severe obstruction than our patients. Taylor and coworkers
assessed the relationship between BHR (assessed at the end of the study (8)) and the
annual decline in FEVi in 227 smoking or ex-smoking men (13). They found that in-
creased BHR (assessed at the end of the study) was related to an accelerated annual
decline in FEVi in smokers but not in ex-smokers. It is not clear from their study if
they controlled for the initial FEVi level and other possible confounding factors. Re-
cently, Hopp et al. demonstrated that enhanced reactivity to methacholine preceded
the onset of clinical asthma (33). Although their study is not comparable with ours
(asthmatic subjects were older and had more airway obstruction), it also suggested
that BHR is a risk factor in the development of asthma. In a recent review, Burrows
and Martinez concluded that existing data do not indicate that BHR is a risk factor
for COPD (34).

The relation between the annual change in BHR and the annual decline in lung
function has been studied even less than the relationship between the initial PC20 and
the annual decline in lung function. Short-term trials with inhaled corticosteroids in
asthma demonstrated that improvements in BHR by steroids were generally not re-
lated to the increases in lung function (35-38). No conclusions can be drawn from
these short-term trials with corticosteroids, but they suggested that the course of
BHR in asthma was independent of the development of airway obstruction. In a pros-
pective study with smokers and ex-smokers, Lim et al. observed that changes in
PC20-histamine over four years were significantly related to the changes in FEVi
(39). This indicated the importance of baseline airway geometry for the PC20 in these
subjects. Although it is not mentioned whether these subjects had COPD, smoking
and airway obstruction were present in most subjects and a history of asthma excluded.

Data on the present study are in accordance with these latest suggestions and observations. The BHR as assessed with the PC_{20}-histamine appeared to be a risk factor in asthma, but not in COPD. This may indicate a different pathogenetic mechanism and the existence of at least two separate diseases (40).

It was concluded that BHR in asthma is involved in the progression of airway obstruction. However, in the COPD patients of the present study, BHR is not a risk factor for the annual decline in ventilatory function, but it reflects the degree of existing airway obstruction.

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55


6. Inhaled beclomethasone improves the long-term course of asthma and COPD in comparison with bronchodilator therapy alone

A prospective controlled study with beclomethasone dipropionate, salbutamol and ipratropium bromide during three years*

Abstract
The effects of inhaled beclomethasone dipropionate (BDP) of 800 μg daily on the long-term course of asthma and Chronic Obstructive Pulmonary Disease (COPD) were investigated in a prospective controlled study during three years. During the first two years, patients were only treated with a bronchodilator (salbutamol or ipratropium bromide). 56 Patients (28 asthma, 28 COPD) with an unfavourable course of disease during bronchodilator therapy alone (an annual decline in the forced expiratory volume in one second (FEV₁) of at least 80 ml/yr in combination with at least one exacerbation/yr) were selected for additional treatment with inhaled beclomethasone of 800 μg daily during the third year. The FEV₁ and the provoking concentration of histamine that induces a 20% fall in FEV₁ (PC₂₀) were assessed at six-month intervals.

In asthma, the annual decline in prebronchodilator FEV₁ of -158 ml/yr during bronchodilator therapy alone was followed by a significant increase of +562 ml/yr during the months 1-6 of BDP treatment (p<0.0005). During the months 7-12 of BDP, the FEV₁ declined slightly with 31 ml/yr which was not statistically different from the annual decline before steroid therapy (p=0.17). In COPD, the increase of +323 ml/yr during the months 1-6 of treatment with BDP was different from the annual decline of -156 ml/yr before BDP (p<0.05). The PC₂₀-histamine improved by 3.8 doubling doses during the months 1-12 of treatment with BDP in asthma (p<0.05) but not in COPD. The weekly measured peak-flow rate (PEFR) improved by 16.7% from the value at the start of BDP therapy in asthma (p<0.0009) and 4.5% in COPD (p<0.05). In comparison with bronchodilator therapy alone, the number of exacerbations decreased by 0.7/yr in asthma (p<0.0001) but not in COPD. In both asthma and COPD, the diurnal variation of the PEFR and the severity of weekly recorded symptoms diminished during BDP treatment (p<0.05).

It was concluded that inhaled BDP of 800 μg daily improved the course of asthma and COPD in comparison with bronchodilator therapy alone. The effects of BDP in patients with asthma were more pronounced than in COPD.

6.1. Introduction

Both asthma and COPD are progressive diseases at an adult age (1-4). The decline in ventilatory function is on average two to four times higher in patients (1,2) than in random samples of the population (5,6). At an advanced stage of the disease, severe limitations in activities of daily life may occur as a consequence of a low ventilatory capacity (7). Patients with a rapid deterioration of pulmonary function are probably at risk for early disability or death from chronic airway obstruction (8). Some retrospective, uncontrolled studies suggested that corticosteroids might slow down the progression of chronic airway obstruction (9). Unfortunately, this suggestion has never been tested in long-term, prospective, controlled studies. Whether inhaled steroids could improve the course of asthma and COPD in comparison with broncho-

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lator therapy alone was investigated in the present prospective controlled study. At an earlier stage, the patients in this study (28 asthma, 28 COPD) participated in a randomised controlled intervention study with bronchodilators (10-12). During two years of treatment with a bronchodilator alone (salbutamol or ipratropium bromide), patients had demonstrated an average decline in FEV$_1$ of 160 ml/yr in combination with almost two exacerbations/yr. Therefore, in the third year, they were additionally treated with inhaled beclomethasone dipropionate (BDP) of 800 μg daily. In this study, the hypothesis that inhaled BDP is able to decelerate the annual decline in FEV$_1$ in comparison with bronchodilator therapy alone was tested.

6.2. Methods

Patients

An extensive description of the patient selection in the preceding bronchodilator intervention study was given elsewhere (10-12). In short: 29 general practitioners in the catchment area of the Nijmegen University were asked to select all their patients of 30 years and above with symptoms of asthma and COPD. Only those patients who showed mild to moderate airway obstruction (FEV$_1$ ≤ FEV$_1$ %predicted (13) minus two standard deviations, but larger than 50% of the predicted value) and/or bronchial hyperresponsiveness to histamine (PC$_{20}$ ≤ 8 mg/ml) were included by the investigators. Patients, dependent on inhaled corticosteroids, with chronic heart failure, with malignant disorders or other severe life-threatening diseases were excluded. One hundred and sixty patients completed the bronchodilator trial. During the two years of bronchodilator treatment, a rapid decline in FEV$_1$ (>80 ml/yr) and a relatively high exacerbation rate (≥1 per year) was observed in a subgroup of 56 patients (=35%). These patients were selected for additional treatment with inhaled BDP in the third year. The detailed selection criteria are shown in Table 6.1. The criteria for diagnosis of asthma or COPD were based on the standards of the American Thoracic Society (7). Asthma was defined as the combination of (10-12): 1. Bronchial hyperresponsiveness to histamine (PC$_{20}$ ≤ 8 mg/ml); 2. Reversible obstruction (FEV$_1$ improved more than 15% of the prebronchodilator value, 60 minutes after the administration of salbutamol 400 μg and ipratropium bromide 80 μg; 3. Dyspnoea; 4. Allergy and/or

| Table 6.1 | Selection criteria of the patients with fast progressive disease, treated with BDP during the third year of study. Patients were selected on the basis of one criteria out of A. and one criteria out of B.: |
| A | an annual decline in FEV$_1$ ≥80 ml/yr, or |
| | FEV$_1$ ≤ FEV$_1$ %predicted – 2 SD and increase in FEV$_1$ ≤10%, 60 minutes after maximal bronchodilatation with salbutamol 400 μg and ipratropium bromide 80 μg, |
| B | number of exacerbations ≥2 per year, or |
| | duration of exacerbation(s) ≥3 weeks per year, or |
| | 1 per year ≤ number of exacerbations <2 per year (but an annual decline in FEV$_1$ ≥120 ml/yr), |
wheezing. COPD was defined as the combination of (10-12): 1. Chronic cough or chronic sputum production in at least three months during at least two consecutive years; 2. Continuous bronchus obstruction (FEV₁ ≤85% of the predicted value).

Although separate features of asthma and COPD were not mutually exclusive (i.e., some asthmatic patients had chronic cough, some COPD patients had a PC20 ≤8 mg/ml), the combination of features was: no patients with asthma could also have COPD and vice versa. The clinical characteristics of the patients are demonstrated in Table 6.2. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.

Table 6.2 Clinical characteristics of the patients with asthma and COPD at the start of the three-year intervention study. Differences between asthma and COPD were statistically compared with the unpaired Student's t-test for normally distributed variables and with the chi-square test for dichotomous variables. Standard deviation between parenthesis (Abbreviations: BDR-FEV₁ is the increase in FEV₁ after bronchodilatation with ipratropium bromide 80 µg and salbutamol 400 µg; DI-PEFR is the diurnal PEFR index).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>49 (12)</td>
<td>54 (2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/16</td>
<td>16/12</td>
</tr>
<tr>
<td>Pack years</td>
<td>13 (14)</td>
<td>*</td>
</tr>
<tr>
<td>Smokers (+/-)</td>
<td>14/14</td>
<td>17/9</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>3 4 (5 3)</td>
<td></td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>14/14</td>
<td>2/24</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>67 (17)</td>
<td>70 (16)</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>57 (15)</td>
<td>63 (13)</td>
</tr>
<tr>
<td>BDR-FEV₁ (%)</td>
<td>14 (9)</td>
<td>*</td>
</tr>
<tr>
<td>DI-PEFR (%)</td>
<td>12 4 (8 0)</td>
<td>†</td>
</tr>
<tr>
<td>PC20 (mg/ml)</td>
<td>0.8</td>
<td>**</td>
</tr>
</tbody>
</table>

* p<0 05, ** p<0.01, *** p<0.001
† p=0.055
# Allergy was defined as at least one positive test out of seven RAST

Study design and treatment
At the start of the three-year intervention study, the patients were randomly allocated to one of the two parallel treatment regimens; continuous or on demand therapy with a bronchodilator. The patients used salbutamol during one year and ipratropium bromide during the other year. The sequence of the drugs was determined by random allocation (10). During the third year, the 56 patients were additionally treated with BDP 800 µg daily in combination with salbutamol 1600 µg or ipratropium bromide 160 µg daily (all dry powder inhalations). The bronchodilator inhaled during the second year was also used in the third year. Once every three months, proper inhalation of the medication as well as compliance to the prescribed medication were checked.

During the first two years of study, 27 of the 56 patients received bronchodilator therapy on demand (15 asthma, 12 COPD). The mean daily dose of salbutamol or ipratropium bromide in the patients treated on demand was 1.2 (SEM 0.3) in asthma, 0.8 (0.2) in COPD. During the third year, 28 patients used salbutamol (15 asthma, 13
COPD), 28 ipratropium bromide (13 asthma, 15 COPD). During the third year, all patients used bronchodilators continuously, during the first and second year only the patients of the continuous treatment group.

**Pulmonary function, non-specific bronchial responsiveness**
The FEV₁, the bronchial responsiveness to histamine (PC₂₀-histamine values) and the reversibility of airway obstruction were assessed at six-month intervals. All measurements were carried out by two qualified laboratory assistants by means of the Microspiro HI-298 (Chest Corporation, Japan) (14). No bronchodilator was inhaled during at least eight hours before the ventilatory function tests. First, dynamic spirometry was performed. The best of three forced expiratory manoeuvres, with the highest sum of the forced vital capacity (FVC) and FEV₁, was used for data analysis. Secondly, bronchial responsiveness to histamine was measured according to the method described by Cockcroft et al. (15). Results were expressed as the provoking concentration of histamine required to produce a 20% fall in FEV₁ (PC₂₀-value). After the FEV₁ had returned to the baseline value, the bronchodilating response was assessed 60 minutes after the administration of ipratropium bromide 80 μg and salbutamol 400 μg (metered dose aerosol). The bronchodilating response was expressed as the relative increase of FEV₁ compared to the predicted value of the FEV₁.

**Peak-flow assessments**
Peak-flow measurements were performed with the Assess peak flow meter in the morning and in the evening, weekly at the same day and time (16). The highest value out of three measurements was taken for analysis. The diurnal PEFR index (absolute difference between evening value and morning value divided by the highest value) was calculated.

**Exacerbations**
Exacerbations were defined according to Fletcher (1) with small modifications of Boman et al. (17). In case of an exacerbation, a ten day course with oral prednisone was given.

**Symptoms and adverse effects**
All patients made weekly recordings of the presence and severity of symptoms (cough, phlegm, dyspnoea) on a scale of 0-4. Adverse effects of medication (dysphonia and oropharyngeal irritation) were recorded by the patients once every three months. Moreover, every six months, the presence and severity of oral candidiasis was assessed by means of a questionnaire.

**Smoking habits**
At the start of the study, the smoking history was assessed retrospectively in pack years. During the study, the average number of cigarettes smoked per day was also recorded in the diary on a weekly basis.
Analysis
Values of outcome variables before the use of BDP were compared with data during steroid treatment. Differences were tested with the paired Student's t-test for normally distributed variables and chi-square test for dichotomous variables. Prior to analysis, the PC_{20} values were $2\log$ transformed. The annual change in FEV$_1$ and PC$_{20}$ was calculated by linear regression of FEV$_1$ and $2\log$PC$_{20}$ in the course of time. A possible influence of the preceding bronchodilator treatment (continuous versus on demand) or of the bronchodilator in the third year (salbutamol versus ipratropium bromide) on the changes in outcome variables during steroid treatment was assessed by multiple analysis of variance (MANOVA).

6.3. Results
Forty-eight of the 56 patients completed one year of treatment with BDP. Reasons for drop-out were: refusal to inhale steroids (1 asthma, 1 COPD), bronchial carcinoma (1 COPD), chronic heart failure (1 COPD), persistent oral candidiasis and dysphonia (1 COPD), serious non-compliance (1 COPD) and personal reasons (1 asthma, 1 COPD).

Asthma
In asthma, the pre- and postbronchodilator FEV$_1$ increased by +0.281(SEM 0.074) liters and +0.100(0.053) liters respectively during the months 1-6 of steroid treatment (p=0.0009 and p=0.070, Figure 6.1). These increases in ml/yr were significantly different from the annual declines measured before steroid treatment (Table 6.3). During the months 7-12 of BDP treatment, the prebronchodilator FEV$_1$ deteriorated slightly with 31 ml/yr but tended to remain different from the annual decline of 158 ml/yr before steroid treatment (p=0.170, Table 6.3). During BDP treatment, the PEFR increased by 16.7(5.7)% and the PC$_{20}$ improved by 3.8(1.4) doubling doses from the value at the start of treatment with BDP (p=0.0009 and p=0.024 respectively, Figures 6.2 and 6.3). The number of exacerbations per year, the severity of symptoms (cough, phlegm and dyspnoea) and the diurnal variation of the PEFR decreased during treatment with BDP (Table 6.3).

COPD
In COPD, the effects of BDP 800 μg daily were less apparent than in asthma. Although the prebronchodilator FEV$_1$ increased by +0.161(SEM 0.091) liters in the first six months of treatment with BDP (this increase was different from the annual decline before the use of BDP, p=0.041), during the months 7-12 the FEV$_1$ decreased by -141 ml/yr (Table 6.3 and Figure 6.1). During the year's treatment with the steroid, the peak flow increased by 4.5(2.3)% whereas the PC$_{20}$ tended to decrease by 1.8(0.9) doubling dose (p=0.055 and p=0.066 respectively, Figures 6.2 and 6.3). The average number of exacerbations per year was not influenced by BDP (Table 6.3). The severity of symptoms decreased during the months 7-12 of treatment (Table 6.3). Moreover, BDP diminished the diurnal variation of the PEFR (Table 6.3).
Table 6.3  Outcome variables in the period before, during 1-6 and 7-12 months of treatment with BDP. The values during BDP therapy were compared with the values before BDP treatment by the paired Student's t-test. The standard errors are between parenthesis. For exacerbations, the value in the whole year of BDP is shown.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment with BDP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Change FEV1-pre (ml/yr)</td>
<td>-158 (26)</td>
</tr>
<tr>
<td>Change FEV1-post (ml/yr)</td>
<td>-115 (23)</td>
</tr>
<tr>
<td>Change PC20 (doubling dose/yr)</td>
<td>-0.38 (0.80)</td>
</tr>
<tr>
<td>Diurnal PEFR index (%)</td>
<td>13.2 (1.6)</td>
</tr>
<tr>
<td>Exacerbations (no /yr)</td>
<td>1.3 (0.2)</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>3.9 (0.8)</td>
</tr>
<tr>
<td>Cough score</td>
<td>0.74 (0.15)</td>
</tr>
<tr>
<td>Phlegm score</td>
<td>0.71 (0.12)</td>
</tr>
<tr>
<td>Dyspnoea score</td>
<td>0.99 (0.17)</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td>Change FEV1-pre (ml/yr)</td>
<td>-156 (26)</td>
</tr>
<tr>
<td>Change FEV1-post (ml/yr)</td>
<td>-77 (23)</td>
</tr>
<tr>
<td>Change PC20 (doubling dose/yr)</td>
<td>-0.51 (0.46)</td>
</tr>
<tr>
<td>Diurnal PEFR index (%)</td>
<td>10.8 (1.4)</td>
</tr>
<tr>
<td>Exacerbations (no /yr)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>Total symptom score</td>
<td>6.2 (0.7)</td>
</tr>
<tr>
<td>Cough score</td>
<td>1.12 (0.17)</td>
</tr>
<tr>
<td>Phlegm score</td>
<td>1.00 (0.10)</td>
</tr>
<tr>
<td>Dyspnoea score</td>
<td>1.52 (0.16)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.005, ***p<0.0005, ****p<0.0001, †p<0.10

Adverse effects
During one year's treatment with steroids, 14% of patients developed oral candidiasis (Chi-square test, p=0.007). Moreover, complaints of dysphonia tended to increase during steroid treatment (Chi-square test, p=0.095).

Influence of bronchodilator therapy preceding and during steroid treatment
No influence of the treatment regimen in the first two years (continuous or on demand) or of the type of bronchodilator (salbutamol or ipratropium bromide) in the third year could be demonstrated on the changes in outcome variables during steroid treatment.

Smoking during the study
In asthma, the proportion of current smokers/non-smokers was 14/14 during the first two years, 11/17 during the third year (p>0.05, two-samples, paired proportion test). Two of the three asthmatics who stopped smoking during the third year had smoked less than 0.1 cigarettes/day during bronchodilator treatment alone. Therefore, these patients were almost non-smokers during the three-year intervention study. In COPD, the proportion of current smokers/non-smokers was 19/9 during the first two years, 18/10 during the third year (p>0.05, two-samples, paired proportion test). One
Figure 6.1 Course of the pre- and postbronchodilator FEV₁ in asthma (top) and COPD during the three years of study. The standard errors of the mean are also represented. Differences in FEV₁ after six and 12 months of treatment with BDP were compared with the initial value at the start of the BDP period (month 24 in the figure) by means of the paired Student's t-test.
Figure 6.2  Course of the PC20 in asthma (top) and COPD during the three years of study. The standard errors of the mean are also represented. Differences in PC20 after six and 12 months of treatment with BDP were compared with the initial value at the start of the BDP period (month 24 in the figure) by means of the paired Student's t-test.
Figure 6.3 Course of the peakflow in asthma (top) and COPD during three years. The peakflow during treatment with BDP was statistically compared with the value just before the start of BDP treatment by means of the paired Student's t-test. The standard errors are also represented.
patient with COPD stopped smoking during the third year. However, this patient was not incorporated in our analysis because of serious non-compliance to BDP.

6.4. Discussion

This study confirmed the hypothesis that daily inhalation of BDP of 800 μg during one year is able to decelerate the decline in FEV₁ during bronchodilator treatment alone in both asthma and COPD. In asthma, steroid treatment during one year even reversed the deterioration during two-year bronchodilator treatment. However, this effect was less apparent in patients with COPD.

Study design
In this self-controlled study, values of outcome measures during bronchodilator therapy alone were compared with the ones during additional inhaled corticosteroid therapy (within-patient comparison of treatments). This design can produce results that are statistically and clinically valid when no period ('natural variation') or carry-over effects (influence of preceding medication) are present (18). Our study meets these criteria for a valid self-controlled design. Therefore, from a methodological point of view, a placebo group was not absolutely necessary in this trial and (more importantly) from an ethical point of view even unacceptable. It is unethical to treat patients with an annual decline in FEV₁ of 160 ml/yr and almost two exacerbations per year with a placebo. In our study, no carry-over effect of the preceding bronchodilator medication in either of the outcome variables during steroid treatment could be demonstrated. No period effect was assessed in the number of exacerbations. Neither in COPD patients who were treated with BDP nor in the other COPD patients of the intervention study (treated only with bronchodilators during the third year of study) did a change in exacerbations occur. A period effect in FEV₁ decline is not probable. The within-patient decline was assessed by linear regression of seven measurements of the FEV₁ during two years with a relatively high percentage of explained variance (31%). Moreover, regression-to-the-mean (because of our selection of patients with a decline in FEV₁ of more than 80 ml/yr during bronchodilator therapy alone) did not explain the observed changes in FEV₁ during BDP therapy. We calculated the effect of regression-to-the-mean in annual decline of FEV₁ by means of the equations presented by Gardner et al. and Das et al. (19,20). This effect appeared to be 28(SEM 7) ml/yr in asthma and 28(12) ml/yr in COPD. After adjusting the changes in FEV₁ during BDP therapy for regression-to-the-mean, almost the same results were found (the unadjusted versus adjusted changes in prebronchodilator FEV₁ during the months 1-6 of BDP were +562 and +547 ml/yr in asthma, +323 and +309 ml/yr in COPD respectively). The adjusted changes remained statistically different from the decline before steroid therapy in both asthma and COPD. Therefore, the observed changes in outcome measures were a real reflection of the effects of inhaled BDP treatment.
Effects of corticosteroids

In asthma, the course of the FEV₁, the PEFR and the PC₂₀ improved during BDP treatment in comparison with bronchodilator therapy alone. BDP was also useful in the prevention of exacerbations, the reduction of respiratory symptoms and diminution of the diurnal variation of the PEFR. BDP not only decelerated the annual decline of the FEV₁ in asthma but almost completely reversed the deterioration in pulmonary function and bronchial hyperresponsiveness during the preceding two years. In COPD, the effects of BDP were less apparent. Although an improvement in FEV₁ and PEFR was observed, the PC₂₀ and the number of exacerbations were not influenced by BDP. The steroid did reduce the severity of symptoms and the diurnal variation of the PEFR.

Corticosteroids probably act on various components of the inflammatory response (21,22). They inhibit the release of mediators from macrophages and eosinophils (21), microvascular leakage and influx of inflammatory cells in the lungs. Late and (after prolonged treatment) early responses to allergens are blocked by steroids (22). Several studies in asthma have demonstrated beneficial effects of inhaled steroids on the ventilatory function, bronchial hyperresponsiveness and respiratory symptoms (23-27). The efficacy of corticosteroids in the treatment of COPD is less clear than in asthma (28). This prospective controlled study is the first long-term one showing that an inhaled steroid (BDP) of 800 μg daily during one year has several beneficial effects in patients with COPD. A relatively large increase in FEV₁ was found during the first six months of BDP treatment in COPD. This was followed by a slight (statistically non-significant) fall during the subsequent six months of BDP treatment. Longer follow-up is necessary to evaluate whether this trend proceeds or not. The treatment with BDP in all patients was continued for another year. The differences in efficacy of BDP between asthma and COPD were not caused by a better compliance to BDP in asthma than in COPD. A study of the patient compliance to BDP by counting capsules (single blind) revealed that no difference between asthma and COPD existed in this respect (29). Patients had used on average 82% of the prescribed dose of BDP.

Adverse effects of inhaled steroids

No serious adverse effects are recorded from inhaled corticosteroids (30). With a daily dose below 1,500 μg, no inhibition of the hypophyseal-pituitary-adrenal axis or other systemic effects were observed (21). In fact, dysphonia and oral candidiasis are the most serious side-effects (31). In our study, 14% of the patients suffered from oral candidiasis. When the BDP was inhaled through a spacer device (31), the complaints diminished or disappeared and patients (except one) were able to continue steroid treatment.

Bronchodilator versus anti-inflammatory therapy

In several recent reviews, inhaled corticosteroids have been advocated as a first-line therapy in asthma which should be introduced at an early stage (21,32). Bronchodilators may not influence inflammation, may mask the inflammatory processes by relieving symptoms and may increase the exposure to allergens, cigarette smoke and...
other irritants (10, 11, 21) The findings of our previous study showed that regular versus on demand use of a bronchodilator (salbutamol or ipratropium bromide) without anti-inflammatory medication was accompanied by an accelerated annual decline in ventilatory function in both asthma and COPD (10) These results corresponded to the findings of Sears et al (33) The most important observation of the present study was that deleterious effects of bronchodilator therapy alone during two years were almost completely abolished by additional treatment with BDP during one year in asthma However, in COPD, the adverse effects were only partly reversible Although the two-year deterioration of the ventilatory function and bronchial hyperresponsiveness was reversible in asthma it is advisable to start with inhaled steroids at an early stage of the disease, particularly when the pulmonary function deteriorates rapidly Chronic inflammation may lead to irreversible changes (3) such as hypertrophy of airway smooth muscle and thickening of basement membrane which probably are inhibited by early steroid therapy (21)

It was concluded that inhalation of BDP of 800 μg daily during one year improved the long-term course of asthma and COPD in comparison with bronchodilator therapy alone The effects of BDP were larger in asthma than in COPD

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7. Slowing the deterioration of asthma and COPD during bronchodilator therapy by adding inhaled corticosteroids

A four-year prospective study*

Abstract

Study Objective. To investigate whether deterioration of asthma or COPD during bronchodilator therapy alone could be improved by additional treatment with an inhaled corticosteroid.

Design. A four-year prospective study.

Setting. 29 general practices in the catchment area of the University of Nijmegen.

Patients. 56 Patients (28 asthma, 28 COPD) with an annual decline in the forced expiratory volume in one second (FEV₁) of at least 80 ml/year in combination with at least two exacerbations/year during bronchodilator therapy alone participated.

Intervention. During the first two years, patients were only treated with a bronchodilator (salbutamol 400 μg or ipratropium bromide 40 μg). During the third and fourth year, additional treatment with beclomethasone dipropionate 400 μg, two times daily was given.

Results. A large initial increase in prebronchodilator FEV₁ of +458 ml/yr (95% CL, 233 to 683) during the first six months of beclomethasone treatment was followed by a decrease of -102 ml/yr during months 7-24. The annual decline in FEV₁ during beclomethasone treatment was less than the decline of -160 ml/yr before beclomethasone therapy (difference 58 ml/yr, 95% CL, 2 to 87). Only in asthmatics did beclomethasone treatment improve the bronchial hyperresponsiveness (assessed by the provoking concentration of histamine that produced a 20% fall in FEV₁, PC₂₀) by 3.0 doubling doses/yr (95% CL, 0.8 to 5.2). Besides, beneficial effects of beclomethasone were found on the (diurnal variation of the) weekly measured PEFR, exacerbations and symptoms in both asthma and COPD.

Conclusion. In the 56 patients of this study, additional treatment with beclomethasone of 800 μg daily improved an unfavorable course of disease during bronchodilator therapy alone. However, this effect was more evident in asthmatics than in patients with COPD.

7.1. Introduction

There are indications that morbidity and mortality due to asthma and Chronic Obstructive Pulmonary Disease (COPD) have increased in the last two decades (1,2). One of the explanations might be that bronchodilator therapy without anti-inflammatory medication is related to this increase in morbidity and mortality (3,4). Recently, two independent studies have found adverse effects of regular bronchodilator treatment on control of asthma (5) and the progression of asthma and COPD (6). In our study (6), continuous treatment with a bronchodilator (ipratropium bromide 40 μg or salbutamol 400 μg, four times daily) was accompanied by a much higher annual decline in the forced expiratory volume in one second (FEV₁) than treatment on demand in 160 patients with asthma or COPD. It is unclear whether an unfavorable

* Accepted for publication by Annals of Internal Medicine as. Dompeling E, Van Schayck CP, Van Grunsven PM, Van Herwaarden CLA, Akkermans R, Molema J, Folgering H, Van Weel C Slowing the deterioration of asthma and COPD during bronchodilator therapy by adding inhaled corticosteroids. A four-year prospective study.
course of asthma or COPD during bronchodilator therapy alone can be reversed or decelerated by additional anti-inflammatory therapy with inhaled corticosteroids. The present study deals with 56 of the 160 patients who had an unfavorable course of disease during bronchodilator therapy alone (an annual decline in FEV\textsubscript{1} of at least 80 ml/yr in combination with at least two exacerbations/year). These 56 patients (28 asthma, 28 COPD) were additionally treated with an inhaled steroid (beclomethasone dipropionate 800 μg daily), during the third and fourth year of the study. It was investigated whether the worsening of their disease during bronchodilator therapy alone was reversed or decelerated by additional anti-inflammatory treatment with beclomethasone. The outcome measures were dynamic lung function indices (annual decline in pre- and postbronchodilator FEV\textsubscript{1}, peak-flow rate (PEFR), forced inspiratory volume in one second (FIV\textsubscript{1})), static lung function indices (residual volume (RV), ratio residual volume/total lung capacity (RV/TLC), inspiratory vital capacity (IVC)), nonspecific bronchial responsiveness (PC\textsubscript{20}-histamine), exacerbations and respiratory symptoms.

### 7.2. Methods

**Patients**

An extensive description of the patient selection in the preceding bronchodilator intervention study was given elsewhere (6). In short: 29 family physicians in the catchment area of the Nijmegen University selected all their patients aged 30 years and over with symptoms of asthma and COPD. Only those patients who showed mild to moderate airway obstruction (FEV\textsubscript{1} >50% of the predicted value (7)) and/or bronchial hyperresponsiveness to histamine (provoking concentration of histamine that induces a 20% fall in FEV\textsubscript{1} (PC\textsubscript{20} ≤8 mg/ml) were included by the investigators. Patients dependent on inhaled corticosteroids, with chronic heart failure, with malignant disorders or other severe life-threatening diseases were excluded. Of these patients, 160 (59 asthma, 101 COPD) completed the bronchodilator trial. During the two years of bronchodilator treatment, a rapid decline in FEV\textsubscript{1} (≥80 ml/yr) and a relatively high exacerbation rate (≥1 per year) were observed in a subgroup of 56 patients (35%). These patients with an unfavorable course of disease were selected for additional treatment with inhaled beclomethasone during two years. The criteria for diagnosis of asthma or COPD were based on the standards of the American Thoracic Society (8). Asthma was defined as the combination of (6,8): 1. Bronchial hyperresponsiveness to histamine (PC\textsubscript{20} ≤8 mg/ml); 2. Reversible obstruction (FEV\textsubscript{1} improved by more than 15% of the prebronchodilator value, 60 minutes after the administration of both salbutamol 400 μg and ipratropium bromide 80 μg); 3. Dyspnea; 4. Allergy (which was defined as at least one positive test out of seven radioallergosorbent tests (RAST, Pharmacia, Sweden. Pollen from weeds, grasses, and trees; Cats and dogs; house dust mite; Aspergillus fumigatus)) and/or wheezing. COPD was defined as the combination of (6,8): 1. Chronic cough or chronic sputum production for at least three months during at least two consecutive years; 2. Continuous bronchus obstruction (FEV\textsubscript{1} ≤85% of the predicted value). Although separate features of asthma and
COPD were not mutually exclusive (for instance, some asthmatic patients had chronic cough, some COPD patients had a PC\textsubscript{20} ≤ 8 mg/ml), the combination of features was: no patients with asthma also had COPD and vice versa (6). The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.

**Study design and treatment**

At the start of the four-year intervention study, the patients were randomly allocated to one of the two parallel treatment regimens: continuous bronchodilator therapy (four times daily) or treatment on demand (only dry powder inhalations during periods of complaints) (6). The patients used dry powder inhalations of salbutamol 400 μg (Glaxo, Zeist, The Netherlands) during one year and of ipratropium bromide 40 μg (Boehringer Ingelheim, Alkmaar, The Netherlands) during the other year. The sequence of the drugs was determined by random allocation. During the third and fourth year, the 56 patients were additionally treated with beclomethasone 400 μg (Glaxo, Zeist, The Netherlands), two times daily in combination with salbutamol 400 μg or ipratropium bromide 40 μg, four times daily (all dry powder inhalations). The bronchodilator inhaled during the second year was also used in the third and fourth year.

During the first two years of the study, 27 of the 56 patients received bronchodilator therapy on demand (15 asthma, 12 COPD). The mean daily number of dry powder inhalations of salbutamol or ipratropium bromide in the patients treated on demand was (mean ± SEM) 1.2 ± 0.3 in asthma, 0.8 ± 0.2 in COPD. During the third and fourth year, 28 patients used salbutamol (15 asthma, 13 COPD) and 28 ipratropium bromide (13 asthma, 15 COPD).

Once every three months, the inhalation technique as well as compliance with the prescribed medication were checked. Patients were instructed to rinse their mouth after the dry powder inhalations. During the second year of beclomethasone therapy, a single-blind prospective study was carried out on the patient compliance with beclomethasone and the additional bronchodilator. Compliance was measured by counting capsules at the end of a four-month period. Patients were unaware that their medication was counted after this period.

**Lung function, non-specific bronchial responsiveness and reversibility**

All measurements were carried out by two qualified laboratory assistants during exacerbation-free periods. No bronchodilator was inhaled during at least eight hours before the pulmonary function tests. At the start and after 24 and 48 months of the study, the inspiratory vital capacity (IVC), residual volume (RV), functional residual capacity (FRC) and total lung capacity (TLC) were assessed by means of the wet Gould spirometer according to the standards of the European Coal and Steel Community (ECSC) (7). The FEV\textsubscript{1}, bronchial responsiveness to histamine (PC\textsubscript{20}-histamine values) and the reversibility of airway obstruction were assessed at six-month intervals by means of the Microspiro HI-298 (Chest Corporation, Japan) (9). Moreover, the FEV\textsubscript{1} and the reversibility were also assessed after 1 and 13 months of study (6). The best of three forced expiratory manoeuvres, with the highest sum of the
forced vital capacity (FVC) and FEV₁, was used for data analysis. The bronchial responsiveness to histamine was measured according to the method described by Cockcroft and colleagues (10). Results were expressed as the provoking concentration of histamine that produces a 20% fall in FEV₁ (PC₂₀-value). After the FEV₁ had returned to the baseline value, the bronchodilating response (reversibility) was assessed 60 minutes after the administration of both ipratropium bromide 80 μg and salbutamol 400 μg (metered dose aerosol) (6). The bronchodilating response was expressed as the relative increase of FEV₁ compared to the predicted value of the FEV₁.

Peak expiratory flow assessments
Once a week, peak expiratory flow (PEFR) measurements were performed with the Assess peak flow meter (11) in the morning and in the evening, on the same day and at the same time. The highest value out of three measurements was taken for analysis. The diurnal PEFR index (absolute difference between evening value and morning value divided by the highest value) was calculated.

Exacerbations
Exacerbations were defined according to Fletcher with small modifications of Boman and colleagues (12). In case of an exacerbation, a ten-day course with oral prednisone was given. Patients received 25 mg for two days, 20 mg for two days, 15 mg for two days, and so on.

Symptoms and adverse effects
All patients made weekly recordings of the presence and severity of symptoms (cough, phlegm, dyspnea, fatigue, disturbed sleep at night) on a scale of 0-4. Adverse effects of medication (dysphonia and oropharyngeal irritation) were recorded by the patients once every three months. Moreover, every six months, the presence and severity of oral candidiasis was assessed by means of a questionnaire (no, light or severe complaints).

Smoking habits
At the start of the study, the smoking history was assessed in pack years. During the study, the average number of cigarettes smoked per day was also recorded in the diary every week.

Power calculations
Assuming that the clinically relevant, decreased annual decline in FEV₁ during beclomethasone treatment is 25 ml/yr and the residual standard deviation 50 ml/yr, the CV (coefficient of variation) is 25/50=0.5. With an α of 0.05 and a β of 0.20 (power of (1-0.2)=0.8), the required number of patients is 51. With an estimated drop-out rate of 10%, the required initial number of patients is 56.

Analysis
Values of outcome variables before the use of beclomethasone were compared with data during beclomethasone treatment. Differences were tested by repeated measures
analysis of variance and the paired Student’s t-test for normally distributed variables, the Wilcoxon paired signed-rank test for not normally distributed variables. Prior to analysis, the PC20 values were $\log$ transformed. The annual changes in FEV$_1$ and PC20 were calculated by linear regression of individual FEV$_1$ and $\log$PC$_{20}$ values in the course of time. For values in groups, the individual regression coefficients were averaged. The weekly measured PEFR was averaged for three-month periods and statistically compared with the value just before the start of beclomethasone therapy. Patients with asthma and COPD were analyzed together and separately.

The gain in FEV$_1$ caused by two-year additional treatment with beclomethasone was calculated. This was done by comparing the end-point of FEV$_1$ after the two-year treatment with beclomethasone with the extrapolated end-point if bronchodilator therapy alone had been continued during the third and fourth year (point E in Figure 7.1). Because some degree of spontaneous improvement might have occurred during the third and fourth years if beclomethasone had not been administered, we adjusted the extrapolated end-point E for the disturbing influence of regression to the mean (point E’ in Figure 7.1). The effect of regression to the mean was calculated by the equations of Gardner and colleagues and Das and colleagues (13,14). The gain in FEV$_1$ with and without correction for regression to the mean was calculated.

Figure 7.1 Course of the pre- and postbronchodilator FEV$_1$ during four years in the group as a whole (n=48)*

* BDP = beclomethasone dipropionate, FEV$_1$ = forced expiratory volume in one second, E = the extrapolated end-point if bronchodilator therapy alone had been continued during the third and fourth year, E’ = the extrapolated end-point with a correction for regression to the mean, FEV$_1$-pre = prebronchodilator FEV$_1$, FEV$_1$-post = postbronchodilator FEV$_1$
Figure 7.1 continued Course of the pre- and postbronchodilator FEV₁ during four years in asthma (n=26) and in COPD (n=22)

* BDP = beclomethasone dipropionate, FEV₁ = forced expiratory volume in one second  
FEV₁ pre = prebronchodilator FEV₁  
FEV₁-post = postbronchodilator FEV₁
7.3. Results

Baseline characteristics
In comparison with COPD patients, asthmatics had smoked less in the past and also during the study, were more often allergic, had a higher bronchodilating response in FEV₁, had more diurnal variation in peak flow and more bronchial hyperresponsiveness at the start of the four-year intervention study (Table 7.1). Of the 9 non-smokers with COPD at the start of the four-year study, 6 were ex-smokers. Only 3 COPD patients had never smoked.

Table 7.1 Clinical characteristics of the patients with asthma and COPD at the start of the four-year intervention study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Age, yr</td>
<td>49 ± 12</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>12/16</td>
<td>16/12</td>
</tr>
<tr>
<td>Pack years, n</td>
<td>13 ± 14</td>
<td>*</td>
</tr>
<tr>
<td>Smokers, +/-</td>
<td>14/14</td>
<td>19/9</td>
</tr>
<tr>
<td>Cigarettes/day, n</td>
<td>4 ± 6 7</td>
<td>*</td>
</tr>
<tr>
<td>Allergy, +/-</td>
<td>14/14</td>
<td>2/24</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>67 ± 17</td>
<td>70 ± 16</td>
</tr>
<tr>
<td>FEV₁/IVC, %</td>
<td>57 ± 15</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Reversibility, % FEV₁ predicted</td>
<td>14 ± 9</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>Diurnal PEFR index, %</td>
<td>12 ± 8</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>PC₂₀, mg/ml</td>
<td>0 8</td>
<td>6 2</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.001, † p=0.057
† absolute numbers or mean ± SD

Drop-outs
Of the 56 patients, 48 completed two-year treatment with beclomethasone. Reasons for dropping out were: refusal to use corticosteroids (1 asthma, 1 COPD), bronchial carcinoma (1 COPD), chronic heart failure (1 COPD), persistent oral candidiasis and dysphonia (2 COPD) and personal reasons (1 asthma, 1 COPD).

Compliance
The single-blind study about the patient compliance with medication showed that individual compliance rates (mean ± SD) were on average 82 ± 30% for the prescribed amount of beclomethasone and 98 ± 29% for the additional bronchodilator. Individual compliance rates were not related to the changes in outcome measures (lung function, bronchial hyperresponsiveness, and exacerbations) during beclomethasone treatment (all p-values >0.35).

FEV₁
Because of the patient selection in this study, the annual decline in pre- and postbronchodilator FEV₁ before steroid treatment was large (see Table 7.2 and Figure 7.1). In the group as a whole, repeated measures analysis of variance demonstrated an overall
Table 7.2 Changes in pre- and postbronchodilator FEV₁ before, during the months 1-6 and the months 7-24 of treatment with beclomethasone

<table>
<thead>
<tr>
<th>Category</th>
<th>Variable</th>
<th>Period of treatment with beclomethasone</th>
<th>Before</th>
<th>1-6 months</th>
<th>7-24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=48)</td>
<td>Change FEV₁-pre†, ml/yr</td>
<td></td>
<td>-160</td>
<td>+458***</td>
<td>-102*</td>
</tr>
<tr>
<td></td>
<td>Change FEV₁-post‡, ml/yr</td>
<td></td>
<td>-98</td>
<td>+105**</td>
<td>-120</td>
</tr>
<tr>
<td>Asthma (n=26)</td>
<td>Change FEV₁-pre†, ml/yr</td>
<td></td>
<td>-173</td>
<td>+562***</td>
<td>-100†</td>
</tr>
<tr>
<td></td>
<td>Change FEV₁-post‡, ml/yr</td>
<td></td>
<td>-115</td>
<td>+201*</td>
<td>-120</td>
</tr>
<tr>
<td>COPD (n=22)</td>
<td>Change FEV₁-pre†, ml/yr</td>
<td></td>
<td>-146</td>
<td>+335*</td>
<td>-104</td>
</tr>
<tr>
<td></td>
<td>Change FEV₁-post‡, ml/yr</td>
<td></td>
<td>-79</td>
<td>-5</td>
<td>-120</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.0001, † p=0.059
† Change FEV₁-pre = annual change in prebronchodilator FEV₁, change FEV₁-post = annual change in postbronchodilator FEV₁
‡ The 'before' column refers to the annual decline in FEV₁ during bronchodilator therapy alone for the period of two years preceding intervention with beclomethasone
§ During months 1-6 of BDP treatment, annualized changes in FEV₁ are shown

The treatment effect of beclomethasone during the third and fourth year with respect to both the pre- and postbronchodilator FEV₁ (p=0.0001 and p=0.01 respectively). The increases in the pre- and postbronchodilator FEV₁ were +458 ml/yr and +105 ml/yr respectively during months 1-6 of beclomethasone therapy, which differed from the preceding annual decreases during bronchodilator therapy alone (difference 618 ml/yr [95% CL, 363 to 873] and 205 ml/yr [95% CL, 56 to 354] respectively) (Table 7.2). After the initial improvement, a decline in the pre- and postbronchodilator FEV₁ was found during month 7-24 of steroid treatment. However, the annual decline in prebronchodilator FEV₁ of -102 ml/yr during months 7-24 of steroid therapy was less than that before steroid treatment (difference 58 ml/yr; 95% CL, 2 to 87) (Table 7.2). Assessing the changes in FEV₁ for patients with asthma and COPD separately, it appeared that the effects of beclomethasone were more pronounced in asthma than in COPD (Table 7.2).

The gain in prebronchodilator FEV₁ (adjusted for regression to the mean) was +0.36 liter in asthma (95% CL, 0.20 to 0.52) and +0.20 liter in COPD (95% CL, -0.02 to 0.42). No statistically significant gains in postbronchodilator FEV₁ values were observed. The effects of beclomethasone with and without correction for regression to the mean were the same.

PEFR
During the whole treatment period with beclomethasone in asthmatics, the PEFR significantly improved compared to the value at the start of beclomethasone treatment with a maximal increase (mean ± SEM) of 0.7 ± 0.2 L/s during months 13-15 of beclomethasone treatment (p=0.0006). The diurnal variation of the PEFR in asthmatics diminished from 13.2% in the preceding period of bronchodilator therapy alone to 9.7% during month 4-24 of beclomethasone treatment (p=0.017). In patients with COPD, the PEFR increased (mean ± SEM) by 0.21 ± 0.09 L/s compared to the value
at the start of steroid treatment during month 4-9 of beclomethasone treatment (p=0.039), which was not the case during the rest of the beclomethasone treatment period. In COPD, the diurnal variation of the PEFR decreased from 10.7% in the preceding period of bronchodilator therapy alone to 8.4% during month 4-24 of beclomethasone therapy (p=0.0004).

**Other lung function indices**

In asthma, beclomethasone not only improved the course of the forced expiratory flows but also of several other lung function indices (*Table 7.3*). In comparison with bronchodilator therapy alone, the RV decreased by 0.49 L (95% CL, 0.18 to 0.80), the RV/TLC ratio diminished by 9% (95% CL, 3 to 15), the IVC increased by 0.50 L (95% CL, 0.16 to 0.86) and the FIV\textsubscript{1} increased by 0.41 L (95% CL, 0.10 to 0.72) during treatment with beclomethasone. In COPD, no statistically significant changes were found (*Table 7.3*).

**Table 7.3 Change in static lung function indices and forced inspiratory volume in one second (FIV\textsubscript{1}) before and during the use of beclomethasone treatment †**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Change in</th>
<th>Before beclomethasone</th>
<th>During beclomethasone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>TLC, L</td>
<td>-0.158 ± 0.091</td>
<td>-0.169 ± 0.112</td>
<td>0.95</td>
</tr>
<tr>
<td>(n=26)</td>
<td>FRC, L</td>
<td>+0.040 ± 0.081</td>
<td>-0.227 ± 0.106</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>RV, L</td>
<td>+0.166 ± 0.077</td>
<td>-0.331 ± 0.101</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>RV/TLC, %</td>
<td>+4.0 ± 1.5</td>
<td>-4.7 ± 1.7</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>IVC, L</td>
<td>-0.339 ± 0.096</td>
<td>+0.161 ± 0.105</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td>FIV\textsubscript{1}, L</td>
<td>-0.169 ± 0.086</td>
<td>+0.189 ± 0.099</td>
<td>0.019</td>
</tr>
<tr>
<td>COPD</td>
<td>TLC, L</td>
<td>+0.077 ± 0.155</td>
<td>-0.074 ± 0.123</td>
<td>0.56</td>
</tr>
<tr>
<td>(n=22)</td>
<td>FRC, L</td>
<td>+0.134 ± 0.132</td>
<td>-0.097 ± 0.102</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>RV, L</td>
<td>+0.210 ± 0.150</td>
<td>-0.018 ± 0.106</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>RV/TLC, %</td>
<td>+1.4 ± 1.3</td>
<td>-0.7 ± 0.9</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>IVC, L</td>
<td>-0.140 ± 0.061</td>
<td>-0.055 ± 0.082</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>FIV\textsubscript{1}, L</td>
<td>-0.179 ± 0.059</td>
<td>+0.003 ± 0.077</td>
<td>0.15</td>
</tr>
</tbody>
</table>

† Mean values ± SEM are presented

**PC\textsubscript{20}**

The course of the PC\textsubscript{20} is shown in *Figure 7.2*. In asthma, the course of the PC\textsubscript{20} improved by 3.0 doubling doses/yr during beclomethasone treatment in comparison with bronchodilator therapy alone (95% CL, 0.8 to 5.2). In COPD, however, the PC\textsubscript{20} showed no significant change. The annual change of -0.3 doubling dose/yr before beclomethasone therapy was not different from the value of -1.6 doubling dose/yr during beclomethasone treatment (p=0.24) (*Figure 7.2*).

**Exacerbations**

In asthma, the number of exacerbations decreased from 1.3 per year before beclomethasone to 0.6 during beclomethasone therapy (difference 0.7; 95% CL, 0.4 to 1.0). In the first year of beclomethasone treatment, the duration of exacerbations decreased from 1.2 to 0.4 weeks/year (difference 0.8; 95% CL, 0.5 to 1.1). In COPD,
Figure 7.2 Course of the PC20-histamine during four years in asthma (n=26) (top) and in COPD (n=22)*

* BDP = beclomethasone dipropionate
the number of exacerbations diminished from 1.7 to 1.3 per year in the second year of beclomethasone treatment (difference 0.5; 95% CL, 0.1 to 0.9).

**Symptoms**
In asthma, the severity of weekly recorded total symptoms showed a decrease of 17% during the first three months of beclomethasone compared to the period before beclomethasone treatment (p=0.01). This also appeared to be the case for the dyspnea score (19%, p=0.054) and the cough score (28%, p=0.005). During the rest of the treatment period, no significant improvements were found for the total symptom score. In COPD, the severity of cough, phlegm and dyspnea was only reduced during month 7-12 of beclomethasone treatment (13%, p=0.033).

**Adverse effects**
On average, no increase in the severity of dysphonia and irritation of the oropharynx were found during treatment with beclomethasone in comparison with the severity just before treatment, neither in the group as a whole (all p-values >0.37) nor in asthma or COPD separately. However, the severity of oral candidiasis increased after one year of beclomethasone therapy compared to the value at the start of steroid treatment (score 0.21 versus 0.02, p=0.01). On account of oral candidiasis, 6 patients had to use their medication with a spacer. Four patients were able to continue the study with a spacer, 2 dropped out for persistent oral candidiasis and dysphonia.

**Smoking**
In asthma, the proportion of current smokers/non-smokers was 14/14 during the first two years, 12/16 during the third and fourth year (p>0.05, two samples paired proportion test). Two of the three asthmatics who stopped smoking had smoked less than 0.1 cigarettes/day during bronchodilator therapy alone. Therefore, these patients can be regarded as non-smokers during the four-year study period. One asthmatic patient started smoking during beclomethasone therapy. In COPD, the proportion of current smokers/non-smokers was 19/9 during the first two years, 17/11 during beclomethasone treatment (p>0.05, two samples, paired proportion test). One of the two COPD patients who stopped smoking during beclomethasone therapy dropped out because of personal reasons.

**Influence of preceding bronchodilator treatment on the change in outcome measures during beclomethasone therapy**
No influence of the treatment regimen in the first two years (continuous bronchodilator therapy or treatment on demand) or of the sequence of the bronchodilators during this study period (salbutamol-ipratropium bromide or ipratropium bromide-salbutamol) on the changes in outcome measures during beclomethasone therapy was found.

**Delay in reaching severe airflow obstruction**
It is very useful to know to what extent inhaled corticosteroids can induce a delay in reaching a certain low level of lung function (severe degree of chronic airflow limitation). It is possible to get an impression of this topic by simple calculations from the
Figure 7.3 A theoretical comparison in the group as a whole between the effects of beclomethasone therapy and ongoing bronchodilator therapy on the time (in years) before reaching a certain severe degree of chronic airflow limitation on the basis of the extrapolated data in this study*

\[ \text{FEV}_1 \ (L) \]

---

\[ \text{Time (yrs)} \]

---

\[ \text{without steroids} \]

\[ \text{with steroids} \]

---

* The prebronchodilator FEV\textsubscript{1} at the start of the four-year intervention study was 2.07 liters, the annual decline without inhaled steroids 0.160 liter/year and with steroids 0.100 liter/year (both asthmatics and COPD patients). It is assumed that the annual decline in FEV\textsubscript{1} is stable in the course of time. Time (X) before level of 1.0 L is reached without intervention with steroids \( X = (2.07 - 1.0) / 0.160 = 6.7 \) years, and with steroid intervention \( X' = 0.5 + \left( 2.07 + 0.23 - 1.0 / 0.100 \right) = 13.5 \) years (0.5 is the delay because of the rise in FEV\textsubscript{1} during months 1-6 of beclomethasone, 0.23 is the absolute increase in FEV\textsubscript{1} during this period). Time (Y) before FEV\textsubscript{1} level of 0.5 L is reached without intervention with steroids \( Y = (2.07 - 0.5) / 0.160 = 9.8 \) years and with steroid intervention \( Y' = 0.5 + \left( 2.07 + 0.23 - 0.5 / 0.10 \right) = 18.5 \) years. It appears that intervention with steroids almost doubles the time before low levels of lung function (0.5-1.0 L) are reached.

Data in our study. Assuming that the decline in FEV\textsubscript{1} in the course of 10 to 20 years is stable, it can be calculated that the time in years before a certain (low) FEV\textsubscript{1} level of 0.5 to 1.0 L is reached in our patients population is almost doubled when inhaled steroids are substituted (Figure 7.3).

7.4. Discussion

Crossover and self-controlled study designs can produce results that statistically and clinically are as valid as the parallel study design, even with a lower required number of patients (15). However, two conditions have to be fulfilled: no period or carry-over effects should be present. In our study, no carry-over effect of the preceding bronchodilator medication on either of the outcome measures during beclomethasone treatment was found. No period effect was assessed in the number of exacerbations and the FEV\textsubscript{1} decline. We can assume that the decline in FEV\textsubscript{1} would have continued if patients had not received additional beclomethasone during the third and fourth year. There are three reasons for this assumption: 1) a stable annual decline in FEV\textsubscript{1}
during a period of several years (linear loss of FEV$_1$ in the course of time) was invariably found in studies on patients (16-19) or on random population samples (20-23); 2) in the 56 patients of this study, the annual decline in FEV$_1$ during bronchodilator therapy alone was stable. The decline during the first year was (mean ± SEM) -149 ± 42 ml/year and the one during the second year -156 ± 60 ml/year, which is comparable; 3) regression to the mean did not explain the observed improvement in FEV$_1$ during beclomethasone therapy. No change in exacerbations occurred during the four-year study period in the other patients of the intervention study, who continued bronchodilator treatment during the third and fourth year of study. Our study meets the criteria for a valid self-controlled trial. Therefore, from a methodological point of view, a placebo group was not absolutely necessary and, more important, from an ethical point of view this would even be unacceptable. It is unethical to treat patients who showed an average annual decline in FEV$_1$ of 160 ml/yr and almost two exacerbations per year, with a placebo. The observed improvements in outcome measures during the third and fourth year of study must have been the result of additional beclomethasone therapy.

Our study shows that in the 56 patients with asthma or COPD, additional treatment with an inhaled corticosteroid (beclomethasone) of 800 μg daily during two years improves the unfavorable course of disease during bronchodilator treatment alone. The increase in FEV$_1$ reached a plateau during the first six months of beclomethasone treatment after which a decline in FEV$_1$ was found. However, the annual decline in FEV$_1$ during month 7-24 of beclomethasone treatment was significantly less than the decline during bronchodilator therapy alone. The large improvement in FEV$_1$ during the first six months of beclomethasone treatment probably is the consequence of a rapid initial decrease in the thickness of airway mucosa and submucosa by inhibition of oedema, microvascular leakage and mucus production from glands. The inflammatory processes underlying asthma or COPD in this study are probably not completely abolished by beclomethasone treatment as the annual decline in FEV$_1$ during months 7-24 of beclomethasone treatment was still larger than the physiological decline of 20-40 ml/yr found in random population samples. Nevertheless, these findings indicate that inhaled corticosteroids not only have a short-term influence during several months but also a long-term influence during two or more years. The clinically significant gain in FEV$_1$ after two-year treatment with beclomethasone demonstrated that patients were in a more favorable clinical condition than they would have been if bronchodilator treatment alone had been continued for another two years. This gain was not statistically significant in the separate group of 22 patients with COPD. In our power analysis, we assumed an influence of beclomethasone on the annual decline in FEV$_1$ in asthmatics as well as patients with COPD. Only in the whole group of 56 patients, we had sufficient statistical power to demonstrate that the annual decline in FEV$_1$ during beclomethasone treatment was statistically significant less than before steroid therapy. The data suggest that this effect may be more evident in asthmatics (70 ml/yr) than in patients with COPD (50 ml/yr). Finally, our calculations showed that inhaled beclomethasone may double the time before reaching low levels of lung function of 0.5 to 1.0 L (Figure 7.3). Of course, this is a simplification based on extrapolation for a period of 10 to 20 years but it gives an
impression of the delay inhaled corticosteroids might induce in reaching severe
degrees of chronic airflow limitation.

Apart from the effects on the FEV₁, there were beneficial effects of beclometha­
sone on static lung function indices and nonspecific bronchial responsiveness (not in
COPD patients), peak-flow rate, exacerbations and respiratory symptoms. The peak
flow was significantly increased during the whole beclomethasone treatment period
in asthma, but in COPD only during months 4-9. Treatment with beclomethasone had
a beneficial influence on the indices of hyperinflation in asthma (RV, RV/TLC) but
not in COPD. Improvements in these indices may also have a beneficial influence on
the efficacy of gas exchange and may reduce the work of breathing (8). The PC₂₀-his­
tamine, which is an important indicator of the severity (10,24) and perhaps even of
the prognosis of asthma (25), improved in the asthmatics of this study during addi­
tional beclomethasone therapy. The number of exacerbations, an important determi­
nant for the subjective well-being of patients with asthma and COPD (8), decreased
during beclomethasone therapy. The weekly recorded symptoms temporarily dim­
inished during beclomethasone treatment in asthma and COPD. Unfortunately, com­
plaints of oral candidiasis increased during beclomethasone treatment, though most
patients (except two) could continue with beclomethasone when this drug was in­
haled with a spacer. With a spacer, the drug deposition in the oropharynx is dim­
inished and therefore also the severity of local side-effects in this area (26,27).

There are indications that morbidity and mortality due to asthma and COPD have
increased in the past two decades (1,2). It is possible that bronchodilator therapy
without anti-inflammatory medication has contributed to this world-wide trend in
morbidity and mortality. Bronchodilators are very effective in immediately diminish­
ing bronchospasm and therefore in relieving symptoms directly, but they may have
adverse effects on the control or progression of the disease when used continuously
(5,6). Inflammation of the airway wall is a major factor in the pathophysiology of as­
thma (28) and perhaps also of COPD (29), which makes anti-inflammatory treatment
of major importance (30-32). A problem for the long-term treatment with inhaled ste­
roids is patient-compliance. Patients may not notice the long-term improvements in­
duced by corticosteroids. Indeed, in the asthmatics of our study, only a temporary de­
crease in symptoms was found during the two-year beclomethasone therapy. Com­
ppliance with beclomethasone 800 μg, two times daily in our study was rather good,
but lower than with the additional bronchodilator, four times daily. Probably the, on
average, good compliance rate in our study was the reason that we found no relation­
ship between individual compliance rates and the change in outcome measures dur­
ing beclomethasone treatment. However, during "uncontrolled" conditions in clinical
practice, compliance with medication can be much lower (26,27). This stresses the
importance of proper information about prophylactic steroid treatment and the moti­
vation of patients to use their inhaled steroids by physicians.

Some other long-term studies have shown the efficacy of inhaled corticosteroids
in asthma. Haahtela and colleagues reported the results of a two-year randomized
double blind study with budesonide 600 μg, twice daily and terbutaline 375 μg, twice
daily in 103 newly detected asthmatics (33). Budesonide was superior to terbutaline
in its effect on the peak flow, the PC₁₅, respiratory symptoms and the use of rescue
medication. Two recent one-year studies of Juniper and colleagues, one in 32 steroid-dependent asthmatics (34) and the other one in 32 nonsteroid dependent asthmatics (35), have demonstrated that treatment with budesonide during one year induced a gradual improvement in PC$_{20}$, asthma symptoms, exacerbations and bronchodilator use. In the steroid-dependent asthmatics, also an improvement in the FEV$_1$ was found. Our study confirms that inhaled corticosteroids are a first-line therapy of asthma, particularly when the need for bronchodilators is increasing (30-32).

The efficacy of inhaled corticosteroids in the treatment of COPD has long been subject of controversy (8). No prospective long-term controlled studies have been reported, although two retrospective studies suggested a positive influence of corticosteroids on the annual decline in FEV$_1$ (36,37). Several short-term studies found no effects of corticosteroids in COPD, whereas others observed the opposite (38). A recent editorial about the efficacy of systemic corticosteroids in patients with stable COPD suggested that these drugs are potentially of benefit in COPD (38). In the present four-year prospective study, inhaled beclomethasone had a beneficial influence on the course of the FEV$_1$, the (diurnal variation of the) PEFR, the number of exacerbations and the severity of symptoms in patients with COPD. Therefore, a rapid annual decline in FEV$_1$ during bronchodilator therapy alone is probably a good indication that additional treatment with inhaled corticosteroids in patients with COPD is necessary and effective.

We concluded that in the 56 patients of this study, the deterioration of disease during bronchodilator therapy alone improved by additional treatment with beclomethasone of 800 μg daily. This effect was more evident in asthmatics than in patients with COPD.

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8. The relationship between clinical characteristics and the two-year response to an inhaled corticosteroid (beclomethasone dipropionate) in asthma and COPD*

Abstract
The aim of the present study was to investigate which patients with asthma and COPD benefit in particular from a two-year treatment with an inhaled corticosteroid. The relationship between clinical characteristics (sex, age, smoking habits, symptoms, quality of life, allergy, static and dynamic spirometry, bronchodilating response, bronchial responsiveness to histamine) and the two-year response to inhaled beclomethasone dipropionate 400 μg, two times daily was investigated in 56 patients (28 asthma, 28 COPD). All patients had participated in a preceding two-year bronchodilator intervention study. The outcome measures of BDP therapy were the FEV1 (both pre- and postbronchodilator) and the PC20-histamine, which were assessed at six-month intervals. The postbronchodilator FEV1 was assessed one hour after bronchodilatation with salbutamol 400 μg and ipratropium bromide 80 μg. Clinical characteristics measured at the start of treatment with BDP were related to the change in outcome measures during BDP therapy by means of analysis of variance (ANOVA).

In asthmatics, the average increase in FEV1 during BDP therapy was larger in patients with a better bronchodilating response (FEV1-pre: r=0.62, p<0.0001), a higher diurnal peak-flow rate index (FEV1-post r=0.42, p<0.05), a severer degree of bronchial hyperresponsiveness (FEV1-pre r=-0.64, p=0.066), a lower FIV1 (FEV1-post r=0.42, p<0.05), a higher transfer coefficient (FEV1-pre r=0.76, p<0.01) and a larger annual FEV1 decline during bronchodilator therapy alone (FEV1-post r=-0.62, p<0.001). It was not possible to predict the improvement in bronchial hyperresponsiveness to BDP from these clinical characteristics. In COPD, the average increase in FEV1 during BDP treatment was larger in patients with a better bronchodilating response (FEV1-pre r=0.89, p<0.0001), a lower FEV1/IVC (FEV1-pre r=-0.54, p<0.05), and a larger decline in FEV1 during bronchodilator therapy alone (FEV1-pre r=-0.77, p<0.0001). No variables were significantly related to the change in postbronchodilator FEV1 during BDP therapy in COPD.

It was concluded that in asthmatics and patients with COPD the two-year response in FEV1 to inhaled BDP 400 μg two times daily was larger in patients with more reversibility, more initial airway obstruction and a larger annual FEV1 decline during bronchodilator therapy alone. Only in asthmatics the response to inhaled BDP was more pronounced in patients with a greater degree of bronchial hyperresponsiveness, more diurnal variations in peak-flow rate and a higher transfer coefficient.

8.1. Introduction

In the past few years, treatment with inhaled corticosteroids has become increasingly important in asthma (1,2). It appeared that inflammation of the airway wall is a major pathophysiologic mechanism underlying asthma (3) and perhaps also COPD (4). Some long-term studies during one and two years have shown that maintenance treatment with inhaled corticosteroids is beneficial in asthma (5-7). In contrast to asth-
thma, the efficacy and therefore the precise role of corticosteroids is less clear in the treatment of COPD (8,9). However, a meta-analysis of available short-term studies suggested that corticosteroids are also beneficial in COPD (8). It is probable that subgroups of COPD patients will respond adequately to corticosteroids (9). Besides the general finding that corticosteroids are more efficacious in asthma than in COPD, little is known about the relationship between clinical characteristics (i.e. allergy, level of airway obstruction, degree of bronchial hyperresponsiveness etc.) and the long-term response to inhaled corticosteroids in asthma and COPD. It is important to know which patients in particular will benefit from inhaled corticosteroids, because it will increase our understanding of the mechanism of steroid action and it may refine the treatment policy of asthma and COPD. As far as we know, no studies on this subject have been reported in asthma. In COPD, the relationship between various characteristics (the degree of airway obstruction, the bronchodilating response, the day-to-day variation in lung function and sputum or blood eosinophilia) and the response to systemic corticosteroids for a period of a few weeks has been investigated in several studies (10-17). However, no studies on this subject have been reported concerning the long-term response to corticosteroids -for a period of some years- or the response to inhaled corticosteroids. This kind of studies may be even more important because COPD patients may only respond adequately to corticosteroids after six months to two years of therapy (18). Because of the few systemic side-effects, inhaled corticosteroids are preferred to oral corticosteroids in the long-term management of asthma and COPD (19).

Therefore, we assessed the relationship between clinical characteristics (age, allergy, smoking habits, dynamic and static spirometry, reversibility of obstruction, nonspecific bronchial hyperresponsiveness, respiratory symptoms and quality of life) and the two-year response to an inhaled corticosteroid (beclomethasone dipropionate 400 µg two times daily) in 56 patients with asthma or COPD.

8.2. Methods

Patients
Data of 56 patients (28 asthma, 28 COPD) from a four-year intervention study were analyzed. During the first two years of bronchodilator treatment alone (20), 56 of the 160 patients had an annual decline in FEV₁ of at least 80 ml/year and an exacerbation rate of almost two per year. Therefore, these 56 subjects were additionally treated with BDP 400 µg two times daily in the subsequent two years. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent. Of the 56 patients 48 completed two years of treatment with BDP. Reasons for drop-out were: refusal to use inhaled corticosteroids (1 asthma, 1 COPD), bronchial carcinoma (1 COPD), chronic heart failure (1 COPD), persistent oral candidiasis and dysphonia (2 COPD) and personal reasons (1 asthma, 1 COPD).
Study design and treatment
During the two-year treatment period with BDP the 56 patients were either treated with:
(1) BDP 400 μg two times daily and salbutamol 400 μg four times daily or
(2) BDP 400 μg two times daily and ipratropium bromide 40 μg four times daily (all dry powder inhalations).
The type of bronchodilator (salbutamol or ipratropium bromide) depended on the random allocation in the preceding bronchodilator intervention study period. Salbutamol was used by 28 patients (15 asthma, 13 COPD) and ipratropium bromide by the other 28 (13 asthma, 15 COPD). Once every three months, proper inhalation of the medication as well as compliance with the prescribed medication were checked.

Lung function, nonspecific bronchial responsiveness and reversibility
All measurements were carried out by two qualified laboratory technicians. No bronchodilator was inhaled during at least eight hours before the lung function tests. At the start of treatment with BDP, the inspiratory vital capacity (IVC), residual volume (RV) and total lung capacity (TLC) were assessed by means of the wet spirometer (Pulmonet III, Sensormedics, Bilthoven, The Netherlands) according to the standards of the European Coal and Steel Community (ECSC) (21). The FEV₁, bronchial responsiveness to histamine (PC₂₀-histamine values) and the reversibility of airway obstruction were assessed at six-month intervals by means of an integrating flowmeter (Microspiro HI-298, Chest Corporation, Japan). The best of three forced expiratory manoeuvres, with the highest sum of the forced vital capacity (FVC) and FEV₁, was used for data analysis. The bronchial responsiveness to histamine was measured according to the method described by Cockcroft et al (22). Results were expressed as the provoking concentration of histamine that produces a 20% fall in FEV₁ (PC₂₀-value). After the FEV₁ had returned to the baseline value, the bronchodilating response was assessed 60 minutes after the administration of ipratropium bromide 80 μg and salbutamol 400 μg (both metered dose aerosols). The bronchodilating response was expressed as the relative increase of FEV₁ compared to the predicted value of the FEV₁ and as the absolute increase in litres.

Peak-flow assessments
Peak-flow measurements were performed with the Assess peak flow meter on the same day every week, at the same time in the morning and in the evening. The highest value of three measurements was taken for analysis. The diurnal PEFR index (DI-PEFR, absolute difference between evening and morning value divided by the highest value) was calculated from a 12-week period just before the start of the BDP-trial. The coefficient of variation of the weekly measured peak-flow measurements (CV-PEFR) was calculated during the same period of time (SD of measurements divided by the mean value).

Allergy
Allergy was assessed by specific IgE determinations for seven common inhalation allergens (RAST test, Pharmacia, Sweden. Pollen: weeds, grasses, trees; Animals: cats
and dogs; house dust mite; Aspergillus fumigatus). Patients were considered allergic if at least one of the RAST was positive.

**Symptoms**
Respiratory symptoms were assessed at the start of the BDP treatment by means of the Medical Research Council questionnaire (Dutch Version) and quantified by addition in a score of 0-8.

**Quality of life**
Quality of life was assessed at the start of the BDP trial by the Inventory of Subjective Health (ISH) (23). The ISH contains 21 questions related to subjective physical complaints. The overall ISH score is made up by the number of affirmative answers. The more physical complaints are reported, the higher the score.

**Smoking habits**
At the start of the study, the smoking history was assessed in pack years. During the study, the average number of cigarettes smoked per day was also recorded in the diary every week.

**Analysis**
The variables assessed at the start of treatment with BDP were related to the changes in FEV₁ and PC₂₀ during the two-year BDP treatment by means of analysis of variance (ANOVA). The change in PC₂₀ was estimated by linear regression of PC₂₀ in the course of time. As the change in FEV₁ during BDP treatment was non-linear (Figure 7.1, page 75), an average increase in pre- and postbronchodilator FEV₁ during two-year BDP therapy was calculated and related to the clinical characteristics. Correlation coefficients, the estimates and p-values were calculated. Two-tailed p-values <0.05 were considered statistically significant.

**8.3. Results**

**Clinical characteristics**
At the start of the two-year study period with BDP, asthmatics were characterized by a lower number of pack years, a lower number of smokers and of cigarettes smoked per day, more allergic patients, a higher reversibility, a higher coefficient of variation of peak flow and a lower PC₂₀ in comparison with COPD patients (Table 8.1).

**Effects of BDP on the outcome measures in asthma compared to COPD**
BDP significantly improved the course of the prebronchodilator FEV₁ in asthma (p<0.0001) and COPD (p<0.05) in comparison with bronchodilator therapy alone (Figure 7.1, page 75). The average increase in prebronchodilator FEV₁ during BDP therapy in asthma was 0.228 litres which was not statistically different from the increase of 0.098 litres in COPD (Table 8.2). In asthma, there was a small improvement in the postbronchodilator FEV₁ of 0.015 litres, which was not statistically dif-
Table 8.1 The clinical characteristics of the patients with asthma and COPD at the start of the treatment with inhaled BDP. Differences between asthma and COPD were statistically compared by means of the unpaired Student's t-test for normally distributed variables and by the chi-square test for dichotomic variables. Standard errors between parentheses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>51 (2)</td>
<td>54 (2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/16</td>
<td>16/12</td>
</tr>
<tr>
<td>Pack years</td>
<td>13 (3)</td>
<td>*</td>
</tr>
<tr>
<td>Smokers (+/-)</td>
<td>11/17</td>
<td>†</td>
</tr>
<tr>
<td>Cigarettes/day (no)</td>
<td>2.3 (0.7)</td>
<td>**</td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>13/15</td>
<td>***</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>57 (4)</td>
<td>63 (3)</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>51 (2)</td>
<td>57 (3)</td>
</tr>
<tr>
<td>Reversibility FEV₁ (% predicted)</td>
<td>18 (2)</td>
<td>*</td>
</tr>
<tr>
<td>Coefficient of variation PEFR (%)##</td>
<td>8.5 (0.9)</td>
<td>†</td>
</tr>
<tr>
<td>PC₂₀ (mg/ml)###</td>
<td>0.6</td>
<td>8.4</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.005, *** p<0.001, † p=0.055, † p=0.065
# Allergy was defined as at least one positive test out of seven RAST
## coefficient of variation of the weekly measured morning peak-flow during a four-week period at the start of the study
### geometric mean PC₂₀ values are given

Table 8.2 The average increase in FEV₁ and the total change in PC₂₀ (value at the end minus baseline value) during the two-year BDP treatment period. Values in asthma and COPD were statistically compared by the unpaired Student’s t-test. Standard errors of the mean between parentheses.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Asthma</th>
<th>COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁-pre (L)</td>
<td>0.228 (0.068)</td>
<td>0.098 (0.099)</td>
</tr>
<tr>
<td>FEV₁-post (L)</td>
<td>0.015 (0.050)</td>
<td>-0.068 (0.029)</td>
</tr>
<tr>
<td>PC₂₀ (doubling doses)</td>
<td>2.1 (1.7)</td>
<td>*</td>
</tr>
</tbody>
</table>

* p<0.05

Different from the deterioration of 0.068 litres in COPD either (Table 8.2). In asthma, the PC₂₀ gradually improved by 2.1 doubling doses during the two-year study period, whereas in COPD a decrease of 3.2 doubling doses was found during the same period (p<0.05) (Table 8.2).

Asthma

In asthma, a larger average increase in prebronchodilator FEV₁ during BDP therapy was found in patients with a higher reversibility of obstruction, a higher transfer coefficient and a higher annual decline in prebronchodilator FEV₁ during bronchodilator therapy alone (Table 8.3 and Figure 8.1). Tendencies towards a larger average increase in prebronchodilator FEV₁ were found in patients with a higher diurnal peak-flow rate index and a severer degree of bronchial hyperresponsiveness (p=0.052 and p=0.066 respectively) (Table 8.3 and Figure 8.1). The average increase in post-
Table 8.3 The relationship between clinical characteristics and the change in FEV₁ and PC₂₀ during two-year BDP treatment as assessed by ANOVA. The estimate of FEV₁ is given in 10⁻³ L (SEM between parentheses) and that of PC₂₀ in doubling doses per year. For the AD-FEV₁, prebronchodilator FEV₁ values were taken for the relationship with the change in FEV₁-pre and PC₂₀ during BDP treatment, postbronchodilator values for the change in FEV₁-post. For abbreviations, see list of abbreviations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁-pre</th>
<th>p-value</th>
<th>FEV₁-post</th>
<th>p-value</th>
<th>PC₂₀</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack years</td>
<td>-3.2 (5.0)</td>
<td>0.54</td>
<td>-1.5 (3.7)</td>
<td>0.69</td>
<td>0.07 (0.07)</td>
<td>0.29</td>
</tr>
<tr>
<td>Smoking (+/-)</td>
<td>-136 (142)</td>
<td>0.35</td>
<td>-102 (104)</td>
<td>0.33</td>
<td>1.9 (1.8)</td>
<td>0.29</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
<td>220 (131)</td>
<td>0.11</td>
<td>31 (102)</td>
<td>0.76</td>
<td>-2.5 (1.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>-5.0 (3.4)</td>
<td>0.16</td>
<td>-4.3 (2.4)</td>
<td>0.087</td>
<td>0.03 (0.06)</td>
<td>0.59</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>-6.6 (5.2)</td>
<td>0.21</td>
<td>-2.7 (3.9)</td>
<td>0.50</td>
<td>-0.003 (0.07)</td>
<td>0.97</td>
</tr>
<tr>
<td>BDR-FEV₁ (10⁻³ L)</td>
<td>0.76 (0.21)</td>
<td>0.002</td>
<td>0.04 (0.19)</td>
<td>0.84</td>
<td>-0.005 (0.033)</td>
<td>0.12</td>
</tr>
<tr>
<td>FIV₁ (10⁻³ L)</td>
<td>-0.046 (0.079)</td>
<td>0.57</td>
<td>-0.11 (0.05)</td>
<td>0.050</td>
<td>0.0019 (0.001)</td>
<td>0.065</td>
</tr>
<tr>
<td>AD-FEV₁ (10⁻³ L/yr)</td>
<td>1.8 (0.5)</td>
<td>0.001</td>
<td>1.3 (0.3)</td>
<td>0.001</td>
<td>0.007 (0.007)</td>
<td>0.34</td>
</tr>
<tr>
<td>logPC₂₀</td>
<td>-45.6 (20.9)</td>
<td>0.066</td>
<td>-45.8 (22.6)</td>
<td>0.083</td>
<td>-0.4 (0.4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Di-PEFR (%)</td>
<td>13.11 (6.4)</td>
<td>0.052</td>
<td>9.9 (4.6)</td>
<td>0.045</td>
<td>-0.16 (0.09)</td>
<td>0.088</td>
</tr>
<tr>
<td>CV-PEFR (%)</td>
<td>11.7 (15.1)</td>
<td>0.45</td>
<td>15.7 (10.7)</td>
<td>0.16</td>
<td>-0.16 (0.18)</td>
<td>0.38</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>-1.2 (5.8)</td>
<td>0.84</td>
<td>7.3 (4.0)</td>
<td>0.077</td>
<td>-0.02 (0.08)</td>
<td>0.75</td>
</tr>
<tr>
<td>TlVA (mol/s/kPa/ml)</td>
<td>36.2 (10.2)</td>
<td>0.006</td>
<td>8.8 (9.4)</td>
<td>0.37</td>
<td>-0.05 (0.12)</td>
<td>0.69</td>
</tr>
<tr>
<td>MRC-score</td>
<td>-6.3 (39.8)</td>
<td>0.88</td>
<td>11.0 (30)</td>
<td>0.72</td>
<td>-0.05 (0.55)</td>
<td>0.93</td>
</tr>
<tr>
<td>Ish-score</td>
<td>-30.7 (16.7)</td>
<td>0.079</td>
<td>-9.2 (13.0)</td>
<td>0.49</td>
<td>-0.24 (0.13)</td>
<td>0.098</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack years</td>
<td>4.6 (5.1)</td>
<td>0.38</td>
<td>-0.3 (1.7)</td>
<td>0.86</td>
<td>+0.06 (0.04)</td>
<td>0.17</td>
</tr>
<tr>
<td>Smoking (+/-)</td>
<td>319 (176)</td>
<td>0.086</td>
<td>8 (6.3)</td>
<td>0.90</td>
<td>+0.6 (1.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Allergy (+/-)</td>
<td>-81 (430)</td>
<td>0.85</td>
<td>-170 (134)</td>
<td>0.22</td>
<td>not estimable</td>
<td></td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>-81 (5.2)</td>
<td>0.14</td>
<td>-0.3 (1.8)</td>
<td>0.86</td>
<td>0.04 (0.04)</td>
<td>0.35</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>-15.6 (6.0)</td>
<td>0.018</td>
<td>0.6 (2.3)</td>
<td>0.78</td>
<td>-0.043 (0.067)</td>
<td>0.54</td>
</tr>
<tr>
<td>FIV₁ (10⁻³ L)</td>
<td>-0.053 (0.082)</td>
<td>0.52</td>
<td>0.019 (0.045)</td>
<td>0.67</td>
<td>0.003 (0.001)</td>
<td>0.021</td>
</tr>
<tr>
<td>AD-FEV₁ (10⁻³ L/yr)</td>
<td>1.7 (0.3)</td>
<td>0.0001</td>
<td>0.4 (0.3)</td>
<td>0.10</td>
<td>-0.003 (0.004)</td>
<td>0.55</td>
</tr>
<tr>
<td>BDR-FEV₁ (L)</td>
<td>0.95 (0.11)</td>
<td>0.0001</td>
<td>-0.03 (0.08)</td>
<td>0.70</td>
<td>0.002 (0.002)</td>
<td>0.30</td>
</tr>
<tr>
<td>LogPC₂₀</td>
<td>-3.9 (17.7)</td>
<td>0.83</td>
<td>11.1 (13.3)</td>
<td>0.42</td>
<td>-0.3 (0.3)</td>
<td>0.41</td>
</tr>
<tr>
<td>Di-PEFR (%)</td>
<td>6.0 (12.9)</td>
<td>0.65</td>
<td>3.2 (4.2)</td>
<td>0.46</td>
<td>-0.09 (0.10)</td>
<td>0.38</td>
</tr>
<tr>
<td>CV-PEFR (%)</td>
<td>27.7 (29.4)</td>
<td>0.36</td>
<td>11.5 (9.6)</td>
<td>0.25</td>
<td>-0.21 (0.17)</td>
<td>0.25</td>
</tr>
<tr>
<td>RV/TLC (%)</td>
<td>-0.2 (9.3)</td>
<td>0.98</td>
<td>1.9 (3.0)</td>
<td>0.52</td>
<td>-0.14 (0.07)</td>
<td>0.072</td>
</tr>
<tr>
<td>TlVA (mol/s/kPa/ml)</td>
<td>-13.6 (11.4)</td>
<td>0.25</td>
<td>-0.9 (3.9)</td>
<td>0.82</td>
<td>-0.06 (0.12)</td>
<td>0.64</td>
</tr>
<tr>
<td>MRC-score</td>
<td>23.4 (46.8)</td>
<td>0.62</td>
<td>-22 (15)</td>
<td>0.15</td>
<td>-0.49 (0.40)</td>
<td>0.23</td>
</tr>
<tr>
<td>Ish-score</td>
<td>29.9 (18.4)</td>
<td>0.12</td>
<td>-5.0 (6.4)</td>
<td>0.44</td>
<td>0.19 (0.22)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Bronchodilator FEV₁ during BDP was larger in patients with a lower FIV₁, a higher diurnal peak-flow rate index and a faster annual decline in postbronchodilator FEV₁ (Table 8.3 and Figure 8.1). No variables were significantly related to the increase in PC₂₀ during BDP therapy.

COPD
In COPD, the increase in prebronchodilator FEV₁ during BDP treatment was larger in patients with more reversibility of obstruction, more airway obstruction as assessed by the FEV₁/IVC and a larger decline in prebronchodilator FEV₁ before ste-
Figure 8.1 *The influence of the PC20, the diurnal peak-flow rate index, the bronchodilating response on the response in FEV1 during two-year BDP therapy in asthma.*
Figure 8.1 continued

Figure 8.2 The influence of the FEV1/IVC, the bronchodilating response and the annual decline in FEV1 during bronchodilator therapy alone on the response in FEV1 during BDP therapy in patients with COPD.
Figure 8.2 continued

Increase FEV₁-pre during BDP (I)

Increase FEV₁-pre during BDP (I)

r = 0.54
p = 0.018

FEV₁/IVC (%)  

-1.0
-0.5
0
0.5
1.0
1.5

25 35 45 55 65 75

FEV₁/IVC (%)  

-1.0
-0.5
0
0.5
1.0
1.5
2.0

0.5 1.0 1.5 2.0

Bronchodilating response FEV₁ (I)

r = 0.89
p = 0.0001
roid therapy (Table 8.3 and Figure 8.2). No clinical variables at the start of BDP treatment were significantly related to the change in postbronchodilator FEV₁ during two-year BDP therapy. With respect to the PC₂₀, only the FIV₁ was significantly related to the two-year change in PC₂₀.

8.4. Discussion

It has become clear in the last few years that mucosal inflammation is a major pathophysiologic feature of asthma (1-3) and perhaps also of COPD (4). This makes inhaled corticosteroids increasingly important for treatment of asthma (1,2) and (to a smaller extent) COPD. This shift in treatment policy may be strengthened by the possibility that long-term, continuous use of bronchodilators may have adverse effects in both asthma and COPD (20,23,24).

Attempts to characterize clinical features in asthma and COPD related to the response to corticosteroids were limited so far to patients with COPD, who were treated with systemic corticosteroids for a period of a few weeks. In the present study, clinical characteristics in both asthmatics and patients with COPD were related to the two-year response to an inhaled corticosteroid, beclomethasone dipropionate of 800 μg daily. Outcome measures were the average increase in pre- and postbronchodilator lung function (FEV₁) and the improvement in nonspecific bronchial responsiveness (PC₂₀). Before BDP treatment, these 56 patients were treated with bronchodilators alone (20).

In both asthma and COPD, the bronchodilating response at the start of the BDP treatment period, the initial level of airway obstruction and the annual FEV₁ decline in the preceding period of bronchodilator therapy alone were related to the two-year response to inhaled BDP. A better bronchodilating response (more reversibility) was accompanied by a larger average increase in prebronchodilator FEV₁ during BDP treatment. The reversibility on a bronchodilator appeared to predict the possibility of improvement by inhaled corticosteroids. Airways that respond only slightly to bronchodilators in the presence of significant airway obstruction may have some degree of irreversible damage like loss of lung elastic recoil, hypertrophy of airway smooth muscle and thickening of basement membrane, which cannot be reversed, neither by bronchodilators nor by corticosteroids (25,26). In some of the short-term studies on COPD, a significant relationship was found between the bronchodilating response and the response to oral corticosteroids given for some weeks (11,14,16).

In both asthma and COPD, more airway obstruction (as indicated by a lower FIV₁ in asthma and a lower FEV₁/IVC in patients with COPD) was accompanied by a larger increase in FEV₁ during BDP therapy. It is probable that more airway obstruction is accompanied by a larger response in FEV₁ during BDP treatment because of the greater possibility of improvement in these patients. A comparable explanation has been given for the relationship between the bronchodilating response and the prebronchodilator lung function (27). In general, the response to bronchodilators is larger in patients with more initial airway obstruction, particularly when expressed as a percentage of the prebronchodilator value.
The annual FEV₁ decline during bronchodilator therapy alone was an important predictor of the subsequent response in FEV₁ during two-year BDP therapy. Although this relationship may partly be explained by regression-to-the-mean, it is certainly not the only explanation for this relationship. Regression-to-the-mean appeared to explain less than 5% of the changes observed during BDP treatment in asthma and less than 10% in COPD. It is probable that the patients with the largest increase in airway obstruction (and inflammatory processes) during bronchodilator therapy alone will demonstrate the largest improvements in FEV₁ during treatment with the inflammation-reversing corticosteroids. Therefore, in patients with COPD, a large annual decline in FEV₁ in the absence of anti-inflammatory treatment is probably a useful indication for additional treatment with inhaled corticosteroids.

In asthmatics, but not in COPD, the diurnal PEFR index and the PC₂₀ were related to the increase in FEV₁ during BDP treatment. Both bronchial hyperresponsiveness (i.e. PC₂₀ ≤8 mg/ml) and high diurnal variations of the peakflow (i.e. >15%) are important features of asthma (3,28), which are very much related (28) because they both express bronchial lability of the airways of asthmatics. The degree of nonspecific bronchial responsiveness is closely related to the severity of inflammation in asthma (3). In this way, it could be explained that the subjects with severe bronchial hyperresponsiveness demonstrate the largest responses to inhaled corticosteroids. However, neither in this study nor in the short-term study of James et al. was an indication for such a relationship found in the patients with COPD (29). It is possible that bronchial hyperresponsiveness in COPD does not mark inflammation as it does in asthma, and is probably rather an expression of the degree of existing airway obstruction (30).

Asthmatic patients with a low diffusion capacity demonstrated smaller increases in FEV₁ during BDP treatment. A low diffusion capacity in these patients probably indicated the existence of structural changes on an alveolar level (21), as other lung diseases related to a low diffusion capacity (fibrosis, oedema, embolism) were exclusion criteria for participation in this trial. Emphysema was not excluded in our study. This stressed the importance of preventing structural damage to the airways of patients with asthma, because otherwise their disease will not only worsen but they will also become less responsive to corticosteroids in the long run (31).

No clinical features in asthma could significantly predict the two-year improvement in bronchial hyperresponsiveness during inhaled corticosteroid treatment. The only other study in asthma on this topic also found no significant predictors of the improvement in bronchial hyperresponsiveness during eight weeks of treatment with budesonide (32). Absence of significant predictors for the change in PC₂₀ in COPD may be explained by the absence of an overall treatment effect in this outcome measure. A short-term study in patients with COPD also found no positive effect of an inhaled corticosteroid on nonspecific bronchial responsiveness (33).

The influence of allergy on the response to BDP in asthmatics in this study was less pronounced than expected. Allergic asthmatics tended to respond better to BDP than non-allergic patients, but this was not statistically significant (p=0.11). As perhaps not the presence but more the intensity of allergy was related to the corticosteroid response, we also related the total number of positive RAST to the response to
BDP, but there was no relationship with the improvement in FEV\textsubscript{1} or PC\textsubscript{20} during BDP therapy either. Perhaps the absence of a statistically significant influence of allergy on the response to corticosteroids in asthma may be explained by the wide range of anti-inflammatory effects of corticosteroids. They do not only have an effect on eosinophils but also on macrophages, monocytes etc, so that also the non-allergic asthmatics benefit from inhaled corticosteroid therapy. We were not able to assess the possible influence of allergy on the response to BDP in patients with COPD, because we only had two allergic COPD patients in our study.

Current smoking was not related to the response to inhaled BDP, neither in asthma nor in patients with COPD. It is possible that the beneficial effects of BDP diminished the harmful effects of smoking in our patients. However, in an analysis not reported here, we found an influence of the smoking history on the annual FEV\textsubscript{1} decline during BDP therapy in the same study population: patients with a higher number of pack years had a larger decline in FEV\textsubscript{1} than patients with a lower number. This may point to the relevance of the amount and duration of smoking to the long-term response to corticosteroids. More pack years may be accompanied by more (irreversible) damage to the airways and a lower sensitivity to corticosteroids in asthma and COPD.

The symptom score and quality of life scores at the start of the study were not related to the two-year response to BDP, neither in asthma nor in COPD. It is difficult to predict the objective response to corticosteroids on the basis of the experienced symptoms or quality of life. A poor correlation was described in other studies between objective parameters like lung function (or annual decline in lung function) and bronchial hyperresponsiveness on the one hand and the subjective variables of symptoms and quality of life on the other (23,34).

Chronic inflammation of the airways in asthma may cause irreversible changes (1,2). In the present study, indicators of the severity of airway inflammation (the degree of bronchial hyperresponsiveness, the diurnal variation of the peak flow, the annual FEV\textsubscript{1} decline during bronchodilator therapy alone) were related to the response to BDP in asthmatics. Early treatment with inhaled corticosteroids is particularly indicated in these asthmatics with severe airway inflammation, even when symptoms are well controlled by a beta-agonist once or twice daily. In COPD patients of our study, more reversibility, more airway obstruction and a more rapid annual FEV\textsubscript{1} decline during bronchodilator therapy alone were accompanied by a better response to inhaled BDP. In these COPD patients, treatment with inhaled corticosteroids may be indicated, also because of the increased risk on early morbidity and mortality in patients with a low lung function level and a high annual decline in lung function (35,36).

We conclude that in asthmatics or patients with COPD the two-year response in FEV\textsubscript{1} to inhaled BDP 400 µg two times daily was larger in patients with more reversibility, more initial airway obstruction and a larger annual FEV\textsubscript{1} decline during bronchodilator therapy alone. Only in asthmatics the response to inhaled BDP was more pronounced in patients with a greater degree of bronchial hyperresponsiveness, more diurnal variations in peak-flow rate and a higher transfer coefficient.
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34 Josephs LK, Gregg I, Holgate ST. Does nonspecific bronchial responsiveness indicate the severity of asthma? Eur Respir J 1990,3 220-227
9. The influence of inhaled beclomethasone dipropionate on quality of life in patients with asthma or chronic airflow limitation*

Abstract
Relatively little is known about the influence of inhaled corticosteroids on general well being (quality of life) in patients with asthma or chronic airflow limitation. In a four-year prospective controlled study we examined the influence of beclomethasone dipropionate (BDP) 400 μg, two times daily, on quality of life in 56 patients with asthma or chronic airflow limitation in comparison with the effects of BDP on symptoms and lung function. During the first two years, patients only received bronchodilator therapy with salbutamol or ipratropium bromide. For additional treatment with BDP during the third and fourth years 56 patients (28 asthma, 28 chronic airflow limitation) with an annual decline in FEV₁ of at least 80 ml/yr in combination with at least two exacerbations per year were selected.

Quality of life was assessed at the start and after two and four years by means of the Inventory of Subjective Health (ISH) and the Nottingham Health Profile (NHP).

BDP did not improve the ISH score or the six dimensions of the NHP, neither in asthma, nor in chronic airflow limitation. However, BDP significantly improved the course of lung function (the forced expiratory volume in one second, FEV₁) \( (p<0.0001) \) BDP temporarily decreased respiratory symptoms during the first three months of BDP treatment in asthma \( (p<0.01) \) and during months 7-12 in chronic airflow limitation \( (p<0.05) \). A weak correlation was found both cross sectionally and longitudinally between (change in) symptoms and quality of life on the one hand and the (change in) FEV₁ on the other.

It was concluded that BDP did not improve the general well being of patients with asthma or chronic airflow limitation. However, BDP significantly improved the course of lung function and temporarily decreased the severity of symptoms. A possible explanation for these observations is that patients soon get used to different levels of lung function and learn to live with their disease. It is advised that both generic and disease-specific health instruments should be used in future intervention studies and also that quality of life should be measured frequently during the early phase of the intervention, e.g., once every month.

9.1. Introduction

Treatment with inhaled corticosteroids has become increasingly important in asthma or (to a smaller degree) chronic airflow limitation (1-4). Airway inflammation is probably an important pathophysiologic mechanism in asthma and perhaps also in chronic airflow limitation (5,6). Several short-term studies during some months (7-10) and a few long-term studies during one or two years (11-13) in asthma have shown that inhaled steroids are able to improve lung function, nonspecific bronchial responsiveness, symptoms, exacerbations and can reduce the need for bronchodilator therapy. There is less unanimity about the effects of corticosteroids in patients with asthma or chronic airflow limitation.

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stable chronic airflow limitation (14). However, a meta-analysis of available short-term studies (15), a recent short-term trial (3) and a retrospective long-term study (4) suggested that corticosteroids are potentially beneficial in chronic airflow limitation. So far no studies have been published on the effects of inhaled steroids on quality of life in patients with asthma or chronic airflow limitation. However, improving the experienced health of these patients is also an important goal of therapeutic intervention (16).

Patients with asthma and chronic airflow limitation may suffer from breathlessness, exercise limitation, anxiety and depression, and problems related to social activities (1,16-19). The quality of life in patients with asthma or chronic airflow limitation was worse than in subjects of the general population (18,19). It is important to know whether treatment with inhaled corticosteroids does not only improve the clinical outcome measures of asthma or chronic airflow limitation but also the general well-being (quality of life) of patients with these diseases.

We studied the influence of an inhaled corticosteroid (beclomethasone dipropionate, BDP) on the quality of life in 56 patients (28 asthma, 28 chronic airflow limitation) in a prospective controlled study. The influence of BDP on quality of life was compared with the effects on symptoms and lung function.

9.2. Methods

Patients
From a population of 160 patients, 56 (28 asthma, 28 chronic airflow limitation) were selected on the basis of a relatively unfavourable course of disease during bronchodilator therapy alone (an annual decline in FEV₁ of at least 80 ml/year in combination with at least two exacerbations/year) (20). All 160 patients had participated in a two-year bronchodilator intervention trial (21). At the start of the four-year study, 29 general practitioners in the catchment area of the Nijmegen University selected all their patients aged 30 and over with symptoms of asthma and chronic airflow limitation. Only those patients who showed mild to moderate airway obstruction (FEV₁ >50% of the predicted value (22)) and/or bronchial hyperresponsiveness to histamine (PC₂₀ ≤8 mg/ml) were included by the investigators. Patients with chronic heart failure, malignant disorders and/or patients who were dependent on corticosteroids were excluded. The criteria for diagnosis of asthma or chronic airflow limitation were based on the standards of the American Thoracic Society (17,21,23). The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent.

Study design and treatment
This study is of a self-controlled design. Outcome measures during treatment with bronchodilators alone (first two years) were compared with those during additional BDP therapy (third and fourth years of study). At the start of the four-year intervention study, the patients were randomly allocated to one of the two parallel treatment regimens; continuous (four times daily) or on demand (only dry powder inhalations
during periods of complaints) bronchodilator therapy (21). The patients used dry powder inhalations of salbutamol 400 μg during the first year and of ipratropium bromide 40 μg during the second, or vice versa. The sequence of the drugs was determined by random allocation. During the third and fourth year, the 56 patients were additionally treated with BDP 400 μg, two times daily. The bronchodilator inhaled during the second year was also used in the third and fourth years. Once every three months, proper inhalation technique as well as compliance with the prescribed medication were checked.

**Measurements**

- **Baseline characteristics.** At the start of the study, smoking behaviour, allergy, lung function (FEV₁ and FEV₁/IVC), reversibility, diurnal peak-flow rate index and bronchial responsiveness to histamine were assessed.

  Smoking history was assessed in pack years. Current smoking status (smoker/non-smoker) and amount of cigarettes/day were measured. Allergy was assessed by specific IgE determinations for 7 common aero-allergens (RAST, Pharmacia, Sweden. Pollen: weeds, grasses, trees; Animals: cats and dogs; House dust mite; Aspergillus Fumigatus). Patients were considered allergic when at least one of the RAST was positive. Reversibility was assessed by the increase in FEV₁, one hour after the administration of salbutamol 400 μg and ipratropium bromide 80 μg and it was expressed as a percentage of the predicted value of FEV₁. The diurnal peak-flow rate index was determined by the absolute difference between the weekly measured evening and morning peak flow (same day and time of day) divided by the highest value of that day for a period of 4 weeks. Bronchial responsiveness to histamine was measured according to the method of Cockcroft et al. (24) and expressed as the provoking concentration of histamine that produced a 20% fall in FEV₁ (PC₂₀ value).

- **Outcome measures.** Quality of life was measured by completing two questionnaires, viz. the Dutch version of the Nottingham Health Profile (NHP) (19,25-29) and the Inventory of Subjective Health (ISH) (19). The NHP is a generic, self-administered questionnaire designed to measure perceived physical, emotional and social health problems. The emphasis is on the respondent's subjective perception of his or her health status (19,25). The NHP focuses on feelings and emotions, not on changes in behaviour. It consists of two parts of which only part one is used in our study. It contains 38 statements relating to 6 dimensions: physical mobility (8 statements), pain (8 statements), social isolation (5 statements), emotional reactions (9 statements), energy (3 statements) and sleep (5 statements). The statements were taken from interviews with patients suffering from various acute or chronic diseases, and from other health questionnaires like the Sickness Impact Profile. All statements are formulated in such a way that they can be answered by yes or no. McKenna derived their weights from a sample of both patients and healthy subjects using Thurstone's method of perceived health problems (26). Separate NHP dimension scores are presented as a profile, not integrated into an overall score. Although the NHP was originally developed as a survey instrument to measure perceived health status in a population, it has been used extensively in evaluation studies and is claimed to be sensitive to change in disease severity (27-29). The NHP has proved to be reliable and can easily
be administered, with small demands on patient time and effort (25). The higher the score, the more physical complaints are reported. The Inventory of Subjective Health, developed by Dirksen (19), is a generic, commonly used Dutch scale which contains 21 questions related to subjective physical complaints like tiredness, chest and heart problems, gastric problems, indigestion, headache, etc. Most complaints can be grouped according to the organ system they referred to. The remaining ones relate to the overall physical condition. The ISH statements were partly taken from the Cornell Medical Index, completed with statements from expert-interviews about the influence of physical stress on health. The internal consistency and reliability of the ISH are strong and answers do not appear to be influenced by social desirability (19). The overall ISH score is made up by the number of affirmative answers. The more physical complaints are reported, the higher the score. Assessments of the quality of life were repeated after two and after four years of study.

Respiratory symptoms were assessed by means of two questionnaires. Firstly, the questionnaire of the Medical Research Council (MRC) (Dutch version) was used at the start and after two and four years of study (30). A total score (MRC-symptom score) of 0-8 was determined from the answers to eight different questions (20). Secondly, patients made weekly recordings of severity of cough, phlegm and dyspnoea on a scale of 0-4. The separate scores together made up the total symptom score (21).

The FEV₁ was assessed by means of the Microspiro HI-298 (Chest Corporation, Japan) (31). The best of three forced expiratory manoeuvres, with the highest sum of the forced vital capacity (FVC) and FEV₁, was used for data analysis. Assessments of the FEV₁ were repeated at six-month intervals. Besides, the FEV₁ was also measured after one month and 13 months of study.

Analysis
No period or carry-over effects were present in this self-controlled trial (32). Regression-to-the-mean appeared to explain only a small, negligible part of the improvements in FEV₁ during BDP therapy (32). So, this study met the criteria for a valid self-controlled trial (32,33).

The annual decline in FEV₁ during bronchodilator therapy alone was estimated by linear regression of FEV₁ in the course of time. Because of a non-linear change in FEV₁ during BDP treatment, the FEV₁ values at the end of BDP treatment were compared with those at the start. The changes in the quality of life scores before and during BDP treatment were statistically compared by the Wilcoxon matched-pairs signed-ranks test (because the distribution was not normal), changes in FEV₁ by the unpaired Student's t-test. Correlations between the change in quality of life and MRC-score on the one hand and the change in FEV₁ on the other were calculated both before and during BDP therapy (longitudinal analysis). Besides, correlations between quality of life, symptoms and lung function were assessed cross-sectionally (between-patient analysis).

Clinical characteristics of asthmatics and patients with chronic airflow limitation were statistically compared by the unpaired Student's t-test for normally distributed variables, the chi-square test for dichotomous parameters and the Mann-Whitney U-test for continuous, not normally distributed variables.
9.3. Results

Baseline characteristics
At the start of the four-year study, asthmatics were characterized by less past and current smoking, a higher percentage of allergy, a higher reversibility and a more severe bronchial hyperresponsiveness than patients with chronic airflow limitation (Table 9.1). Quality of life as assessed by the ISH score was worse in chronic airflow limitation than in asthma (Table 9.1).

Table 9.1 Clinical characteristics of the patients with asthma and chronic airflow limitation at the start of the four-year intervention study. Differences between asthma and chronic airflow limitation were statistically compared by the unpaired Student's t-test for normally distributed variables, the chi-square test for dichotomous variables and the Mann-Whitney U-test for continuous not-normally distributed variables. SD between parentheses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma</th>
<th>Chronic airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>49 (12)</td>
<td>52 (10)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>12/16</td>
<td>16/12</td>
</tr>
<tr>
<td>Pack years</td>
<td>13 (14)</td>
<td>*</td>
</tr>
<tr>
<td>Smokers (+/-)</td>
<td>14/14</td>
<td>19/9</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>4.2 (6 7)</td>
<td>*</td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>14/14</td>
<td>**</td>
</tr>
<tr>
<td>FEV1 %pred</td>
<td>67 (17)</td>
<td>70 (16)</td>
</tr>
<tr>
<td>FEV1/IVC (%)</td>
<td>57 (15)</td>
<td>63 (13)</td>
</tr>
<tr>
<td>Reversibility FEV1 (% pred)</td>
<td>14 (9)</td>
<td>**</td>
</tr>
<tr>
<td>Diurnal PEFR index (%</td>
<td>12 (8)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>PC20 (mg/ml)##</td>
<td>0.8</td>
<td>6.2</td>
</tr>
<tr>
<td>MRC-symptom score</td>
<td>4.9 (1.8)</td>
<td>5.5 (1.7)</td>
</tr>
<tr>
<td>ISH</td>
<td>6.3 (4.6)</td>
<td>*</td>
</tr>
<tr>
<td>NHP-score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- energy</td>
<td>30.2 (38.7)</td>
<td>35.1 (37.2)</td>
</tr>
<tr>
<td>- pain</td>
<td>12.4 (26.0)</td>
<td>19.1 (28.8)</td>
</tr>
<tr>
<td>- emotions</td>
<td>12.5 (19.3)</td>
<td>15.8 (26.5)</td>
</tr>
<tr>
<td>- sleep</td>
<td>19.2 (29.1)</td>
<td>27.1 (23.9)</td>
</tr>
<tr>
<td>- social isolation</td>
<td>13.7 (27.9)</td>
<td>12.3 (25.6)</td>
</tr>
<tr>
<td>- physical mobility</td>
<td>12.0 (20.9)</td>
<td>12.8 (13.8)</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001
# Allergy was defined as at least one positive test out of seven RAST
## Coefficient of variation of the weekly measured morning peak-flow during a four-week period at the start of the study

Of the 56 patients, 48 completed treatment with BDP. Reasons for dropping out were: refusal to use corticosteroids (1 asthma, 1 chronic airflow limitation), bronchial carcinoma (1 chronic airflow limitation), chronic heart failure (1 chronic airflow limitation), persistent oral candidiasis and dysphonia (2 chronic airflow limitation) and personal (non-medical) reasons (1 asthma, 1 chronic airflow limitation).
Quality of life of study population in comparison with a random sample of the population

Compared with data in the general population (25), quality of life at the start of our study appeared to be impaired in the asthmatics and patients with chronic airflow limitation (Figure 9.1). With the exception of the emotional reaction score and the sleep score of the NHP, the quality of life scores in our patients with asthma or chronic airflow limitation were on average two to three times higher than in the general population (Figure 9.1).

Figure 9.1 Quality-of-life scores in patients with asthma and chronic airflow limitation of this study compared with the general population.

The influence of BDP on quality of life, symptoms and lung function

In Table 9.2, the changes in quality of life, MRC-symptom score and FEV₁ during the two-year study period before the use of BDP and during BDP treatment are shown. No significant changes in the quality-of-life scores were found in asthma, neither before treatment with BDP nor during BDP therapy (all p-values >0.17) (Table 9.2). Also when the changes in quality-of-life scores before BDP treatment were compared with those during BDP therapy, no significant improvements were observed in asthma (Wilcoxon matched-pairs signed-ranks test, all p-values >0.48). Before BDP treatment in chronic airflow limitation, however, the MRC-symptom score, the emotional reaction score and the social isolation score of the NHP improved significantly in spite of a substantial worsening of the FEV₁ (Table 9.2). During BDP therapy, no significant changes in quality of life were found in patients with chronic airflow limitation.

In asthma, the severity of weekly recorded symptoms showed a decrease of 17% during the first three months of treatment with BDP compared to the period before
Table 9.2 Changes in quality-of-life scores, MRC-symptom scores and lung function before and during the use of BDP. SEM between parentheses. A negative change in quality-of-life and MRC-score implies an improvement, a positive sign a deterioration.

<table>
<thead>
<tr>
<th></th>
<th>Before BDP</th>
<th></th>
<th></th>
<th>During BDP</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>change in</td>
<td>p</td>
<td></td>
<td>change in</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>+0.27 (0.49)</td>
<td>0.59</td>
<td></td>
<td>+0.68 (0.66)</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>NHP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- energy</td>
<td>-5.5 (4.0)</td>
<td>0.18</td>
<td></td>
<td>-0.4 (4.8)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>- pain</td>
<td>+1.5 (3.4)</td>
<td>0.66</td>
<td></td>
<td>-0.5 (2.5)</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>- emotional reaction</td>
<td>-1.2 (4.2)</td>
<td>0.78</td>
<td></td>
<td>-0.2 (3.1)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>- sleep</td>
<td>+0.10 (3.8)</td>
<td>0.98</td>
<td></td>
<td>+3.0 (3.7)</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>- social isolation</td>
<td>-2.7 (4.1)</td>
<td>0.51</td>
<td></td>
<td>-0.5 (3.1)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>- physical mobility</td>
<td>-4.3 (3.0)</td>
<td>0.17</td>
<td></td>
<td>-0.5 (2.5)</td>
<td>0.84</td>
<td></td>
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<tr>
<td>MRC-symptom score</td>
<td>-0.12 (0.37)</td>
<td>0.75</td>
<td></td>
<td>-0.24 (0.31)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (ml/yr)</td>
<td>-173 (22)</td>
<td>0.0001</td>
<td></td>
<td>+38 (30)</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

Chronic airflow limitation

<table>
<thead>
<tr>
<th></th>
<th>Before BDP</th>
<th></th>
<th></th>
<th>During BDP</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>change in</td>
<td>p</td>
<td></td>
<td>change in</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>-1.2 (0.6)</td>
<td>0.065</td>
<td></td>
<td>+1.3 (0.9)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>NHP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- energy</td>
<td>-6.8 (4.9)</td>
<td>0.18</td>
<td></td>
<td>+3.4 (6.1)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>- pain</td>
<td>-2.0 (5.1)</td>
<td>0.69</td>
<td></td>
<td>+6.7 (4.7)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>- emotional reaction</td>
<td>-7.3 (2.5)</td>
<td>0.01</td>
<td></td>
<td>+2.4 (2.4)</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>- sleep</td>
<td>+2.6 (4.3)</td>
<td>0.55</td>
<td></td>
<td>+0.8 (7.3)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>- social isolation</td>
<td>-4.4 (2.0)</td>
<td>0.04</td>
<td></td>
<td>+0.3 (3.6)</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>- physical mobility</td>
<td>-1.1 (2.4)</td>
<td>0.64</td>
<td></td>
<td>+2.2 (2.4)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>MRC-symptom score</td>
<td>-1.14 (0.40)</td>
<td>0.009</td>
<td></td>
<td>+0.25 (0.33)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (ml/yr)</td>
<td>-146 (36)</td>
<td>0.0006</td>
<td></td>
<td>-23 (35)</td>
<td>0.52</td>
<td></td>
</tr>
</tbody>
</table>

BDP was given (p<0.01) (Figure 9.2). During the rest of the treatment period, no significant improvements were found for the total symptom score. In chronic airflow limitation, the severity of weekly recorded symptoms was only significantly reduced during months 7-12 of BDP treatment (13%, p<0.05) (Figure 9.2).

Both in asthma and chronic airflow limitation, the course of lung function improved by BDP treatment. The FEV₁ deterioration of -160(SEM 20) ml/yr before BDP differed from the change of +10(23) ml/yr during BDP (paired Student’s t-test, p<0.0001). This effect was more evident in asthmatics (-173 versus +38 ml/yr) than in patients with chronic airflow limitation (-146 versus -23 ml/yr).

Correlation between the change in quality of life or symptoms and the change in lung function

In general, there was only a weak correlation between the change in quality-of-life or MRC-symptom scores on the one hand and the change in FEV₁ on the other, both in asthma and chronic airflow limitation (Table 9.3). The only statistically significant findings were those of the energy score of the NHP. In asthma, the change in the energy score was related to the change in FEV₁ during bronchodilator therapy alone (r=+0.44, p<0.05). In chronic airflow limitation, the change in energy score was related to the change in FEV₁ during additional BDP treatment (r=−0.46, p<0.05).
Figure 9.2 Weekly recorded symptom score at three-month intervals during the four-year study period. Only during the first period of BDP treatment a decrease in symptoms was found, not during the rest of the BDP treatment period.

Correlation between quality of life, symptoms and lung function at cross-sectional assessments
When the quality-of-life and MRC symptom scores were related to the FEV₁ at the start, after two and after four years of study, it appeared that no significant correlations were found, neither in asthma (the absolute value of r ranged from 0.004 to 0.39, p>0.05) nor in chronic airflow limitation (absolute value of r ranged from 0.005 to 0.38, p>0.06).

9.4. Discussion
The most important observation of this study was that BDP significantly improved the course of lung function, but not the quality of life in patients with asthma or chronic airflow limitation. BDP diminished the severity of symptoms only significantly for some months during the first year of BDP treatment. During the rest of the treatment period, no influence on symptoms was found, neither in the weekly recorded symptom score nor in the two-yearly measured MRC-symptom score. The substantial decline in lung function during bronchodilator therapy alone was not ac-
Table 9.3  Correlation between the changes in quality-of-life scores, the MRC-symptom scores and the changes in FEV₁ before and during the use of BDP (within-subject analysis).

<table>
<thead>
<tr>
<th></th>
<th>Before BDP</th>
<th></th>
<th>During BDP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>+0 11</td>
<td>0.59</td>
<td>-0 33</td>
<td>0.10</td>
</tr>
<tr>
<td>NHP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- energy</td>
<td>+0 44</td>
<td>0.023</td>
<td>+0 11</td>
<td>0.60</td>
</tr>
<tr>
<td>- pain</td>
<td>-0 07</td>
<td>0.72</td>
<td>-0 02</td>
<td>0.91</td>
</tr>
<tr>
<td>- emotional reaction</td>
<td>+0 35</td>
<td>0.076</td>
<td>-0 34</td>
<td>0.096</td>
</tr>
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<td>- sleep</td>
<td>-0 34</td>
<td>0.09</td>
<td>+0 26</td>
<td>0.20</td>
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<td>0.14</td>
<td>-0 17</td>
<td>0.42</td>
</tr>
<tr>
<td>- physical mobility</td>
<td>+0 35</td>
<td>0.077</td>
<td>+0 20</td>
<td>0.34</td>
</tr>
<tr>
<td>MRC-symptom score</td>
<td>-0 06</td>
<td>0.75</td>
<td>+0 23</td>
<td>0.25</td>
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<td><strong>Chronic airflow limitation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISH</td>
<td>-0 19</td>
<td>0.39</td>
<td>-0 14</td>
<td>0.57</td>
</tr>
<tr>
<td>NHP</td>
<td></td>
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<td></td>
</tr>
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<td>- energy</td>
<td>-0 18</td>
<td>0.41</td>
<td>-0 46</td>
<td>0.039</td>
</tr>
<tr>
<td>- pain</td>
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<td>0.81</td>
<td>-0 23</td>
<td>0.33</td>
</tr>
<tr>
<td>- emotional reaction</td>
<td>+0 11</td>
<td>0.63</td>
<td>-0 18</td>
<td>0.44</td>
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<tr>
<td>- sleep</td>
<td>-0 29</td>
<td>0.22</td>
<td>-0 15</td>
<td>0.54</td>
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<tr>
<td>- social isolation</td>
<td>-0 22</td>
<td>0.32</td>
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<td>0.44</td>
</tr>
<tr>
<td>- physical mobility</td>
<td>+0 30</td>
<td>0.18</td>
<td>-0 03</td>
<td>0.89</td>
</tr>
<tr>
<td>MRC-symptom score</td>
<td>-0 04</td>
<td>0.85</td>
<td>+0 32</td>
<td>0.14</td>
</tr>
</tbody>
</table>

accompanied by a significant worsening of quality of life in this period. In fact, some of the scores even improved significantly during this part of the trial in patients with chronic airflow limitation. This may be explained by an ‘in care’ effect because of participation in the trial. All these findings together may suggest that patients soon get used to different levels of airway obstruction and learn to live with their disease. Their perception of the severity of their disease may be limited (16). There is no reason to doubt the reliability and validity of the generic health instruments NHP and ISH (19,25-29). The NHP was a useful tool in assessing subjective well-being in patients with hypertension (34), myocardial infarction (35), coxarthrosis (36), stroke (37) and asthma (38). Perhaps we had found a positive effect of BDP on quality of life if we had measured this variable frequently during the first year of BDP, like for symptoms. It is also possible that more disease-specific quality of life scales would have indicated an improvement in quality of life. A disease-specific health instrument possibly has the advantage of covering specific aspects of the clinical disorder under study which are not relevant for a generic well-being scale (39). However, examples of disease-specific quality-of-life scales of asthma or chronic airflow limitation have only recently become available (16,40,41) and experience with these scales is therefore limited. If their asthma or chronic airflow limitation is really important for the patients’ overall experienced subjective well-being, improvement of their disease should also be reflected in generic quality-of-life scales. Therefore, it is advisable to use both generic and disease-specific quality-of-life instruments for fu-
ture trials in asthma and chronic airflow limitation. Quality of life must be measured frequently during the early phase of the intervention, i.e. once every month.

A comparison of the ISH and NHP scores in our patients with asthma and chronic airflow limitation with data from the general population (25) revealed that patients indeed experience their disease as important for their general well-being. Quality of life seemed impaired in asthma and chronic airflow limitation when compared with the general population, although this simple comparison must be interpreted with caution. Most of the quality-of-life scores were two to three times higher in the patients of this study than in samples of the general population. Patients with asthma or chronic airflow limitation may suffer from breathlessness, exercise limitation, anxiety and depression, and problems related to social activities (1,16-19). Quality of life may be more disturbed in patients with chronic airflow limitation than in asthmatics (17). In our study, quality of life as assessed by the ISH was worse in chronic airflow limitation than in asthma. This difference was not found for the six dimensions of the NHP. In chronic airflow limitation, obstruction as well as respiratory complaints are of a sustained, chronic character (17). In asthma, the degree of airflow limitation varies considerably in the course of time and symptom-free intervals may alternate with periods of cough, wheezing and dyspnoea (17). The ISH is particularly directed at chronic physical complaints (19) and it is therefore logical that patients with chronic airflow limitation had a higher ISH score than asthmatics.

We investigated the correlation between the quality-of-life scores, MRC-symptom score and the FEV1 both cross-sectionally and longitudinally. In asthma as well as in chronic airflow limitation, the correlations between lung function and quality-of-life scores were weak with only two significant correlations for the energy score of the NHP. In general, correlations within subjects (longitudinal analysis) were slightly higher than between subjects (cross-sectional analysis). Many other studies found a low correlation between all kinds of quality-of-life scales and the lung function level (18,19,40,42,43). It has been suggested that the attitude to health or disease interferes with the relation between lung function and the results of psychometric tests (44). This general attitude towards health or disease may be the reason that a lower lung function level is not necessarily accompanied by a lower experienced quality of life.

Our study is an example of a self-controlled trial in which different treatments are compared within patients. Crossover and self-controlled study designs can produce results that statistically and clinically are just as valid as the parallel study design provided that no period or carry over effects are present (33). Our study meets these criteria for a valid self-controlled trial (32). No placebo was given to our patients because we considered it unethical to treat patients with an annual decline in FEV1 of 160 ml/yr and almost two exacerbations per year with a placebo. From a methodological point of view, a placebo group was not absolutely necessary, because the treatment during bronchodilator therapy alone was a good control period within each patient. It appeared that regression-to-the-mean did not bias the results of BDP therapy in this trial (32).

We conclude that treatment with BDP (in comparison with bronchodilator treatment alone) did not improve the general well-being of patients with asthma or chronic airflow limitation in spite of a positive influence of BDP on the course of
lung function and a temporary reduction in severity of symptoms in these diseases. Neither the substantial decline in lung function during bronchodilator therapy alone nor the improvement in the course of lung function during BDP therapy were accompanied by corresponding changes in the generic quality-of-life scores. An explanation for these findings may be that patients soon get used to different levels of lung function and learn to live with their disease. We recommend that quality of life in future intervention studies should be measured by generic as well as disease-specific health instruments. During the early phase of the intervention, quality of life must be measured frequently, e.g., once every month.

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Abstract
We investigated compliance and inhaler technique in 50 patients with airway obstruction (26 asthma, 24 chronic bronchitis) being treated with an inhaled steroid (BDP, beclomethasone dipropionate) via a dry powder inhaler (dry powder device Rotahaler). Patients had already participated for one year in a two-year trial of BDP in general practice. They were treated daily with two dry powder inhalations of 400 μg BDP in combination with a bronchodilator (salbutamol or ipratropium bromide). Compliance with BDP was measured by counting capsules (single-blind) at the end of a four-month period and through a questionnaire.

Counting capsules revealed that patients used on average 82 (SD=30)% of the prescribed amount of BDP. Non-compliance (defined as a compliance rate below 80% or above 120%) to BDP was present in 46% of the patients. The questionnaire suggested that only 7% of the patients was non-compliant. Individual compliance rates were not related to age, sex, diagnosis or side-effects of BDP. In chronic bronchitis, but not in asthma, compliance was related to the outcome parameters of steroid treatment (pulmonary symptoms, the change in lung function and nonspecific bronchial responsiveness). The inhaler technique was judged insufficient in 27% of the patients.

This study stresses the importance of regular instruction in inhaler technique and proper information about prophylactic steroid treatment by the general practitioner during the treatment of asthma and chronic bronchitis.

10.1. Introduction
Asthma and chronic bronchitis are considered to be progressive diseases (1,2), which should be treated at an early stage. Since chronic inflammation of the airways seems to play an important role in the pathophysiology of airway obstruction (3), anti-inflammatory drugs, such as inhaled corticosteroids are increasingly being prescribed for prolonged periods (4-6) by GPs. However, the efficacy of such prophylactic therapy not only depends on adequate prescription, but also on a good patient compliance (7,8) and a proper inhaler technique (9). In two short-term controlled studies in asthma, compliance with inhaled steroids were 76 and 85%, respectively (7,8). Although inhaled steroids are mostly described on a long-term basis, no studies have assessed the compliance with long-term inhaled steroid treatment. Dry powder inhalers are being used more frequently in the treatment of airway obstruction: they are easier to handle than the aerosol inhaler, because hand-lung coordination is not necessary in its use (10). In addition, dry powder inhalers do not contain chlorofluorocarbon propellants, and therefore are ozone-friendly devices (10,11). In the few
studies in which the inhaler technique of dry powder devices was assessed, an incor­
correct inhaler technique was demonstrated in 4-54% of the patients (12-14), dependent
on the type of inhaler device and the method of measuring.

The aim of our study was to assess the long-term compliance with beclometha­sone dipropionate (BDP) in moderate asthma and chronic bronchitis and the inhaler technique. Relations between patient compliance on the one hand, and clinical char­acteristics (age, sex, diagnosis) and outcome parameters of treatment with BDP (symptoms, side-effects, exacerbations, lung function, nonspecific bronchial respons­iveness) on the other were also assessed.

10.2. Methods

Patients and study design
Fifty patients with moderate airway obstruction (26 with asthma, 24 with chronic bronchitis), selected from general practice entered this study (Table 10.1). They had already participated for one year in a two-year intervention study with BDP: an ex­tensive description of the patients and study design of the BDP trial are given else­where (15-17). In summary: 56 patients were selected for a two-year trial with BDP and were treated daily with two dry powder inhalations (d.p.i.) of BDP 400 μg in combination with four d.p.i. of a bronchodilator, salbutamol 400 μg or ipratropium bromide 40 μg. BDP was inhaled by the Rotahaler (Glaxo, Netherlands). At the start of the trial with BDP, extensive instructions how to use the Rotahaler had been given by the principle investigator. Lung function (forced expiratory volume in one second, FEV₁) and bronchial responsiveness to histamine (the minimal concentration of his­tamine in mg/ml, necessary to induce a 20% fall in FEV₁, the PC₂₀-histamine) were assessed under standardized circumstances by two laboratory technicians every six months. During these visits any possible problems with the trial medication was dis­cussed and a fixed amount of new medication was provided. Patients had to consult their general practitioner in case of exacerbations (15), and were instructed to keep a

| Table 10.1 Patient characteristics. Standard deviations or ranges are given in parentheses. Differences between asthma and chronic bronchitis were tested by means of the chi-square test for dichotomous variables, by means of the unpaired Student's t-test for continuously distributed variables. |
|----------------------------------|------------------|------------------|
| **Asthma**                      | **Chronic Bronchitis** |
| Number                          | 26               | 24               |
| Age (years)                     | 52 (32-73)       | 55 (39-71)       |
| Sex (M/F)                       | 10/16            | 14/10            |
| Smoker (+/-)                    | 10/16            | *                |
| Pack years (number)             | 12 (14)          | 23 (17)          |
| Allergy (+/-)                   | 13/13            | **               |
| FEV₁ (%pred)                    | 65 (22)          | 63 (18)          |
| PC₂₀ (mg/ml)#                   | 0.07             | **               |

* p<0.05, ** p<0.005, *** p<0.0005
# geometric mean PC₂₀-values are given
weekly report of peak-flow measurements, the severity of pulmonary symptoms (cough, phlegm, dyspnoea) and side-effects of BDP (dysphonia, oropharyngeal irritation, oral candidiasis). The trial was approved by the Ethics Committee of the University of Nijmegen and all patients gave informed consent.

Assessment of compliance and inhaler technique
In the second year of the two-year trial with BDP, compliance to inhaled BDP was measured by counting capsules at the end of a four-month period: Patients were unaware of this. This objective method was considered as the 'golden standard' of measuring compliance. Capsules of salbutamol and ipratropium bromide were also counted. Individual compliance rates with BDP, salbutamol and ipratropium bromide were determined by expressing the number of capsules taken (number of capsules provided minus number of capsules left) as a percentage of the amount prescribed. In addition a standard (anonymous) questionnaire was filled in by the patients at the end of the four-month period. The questionnaire asked: 'Did you miss or overuse more than 10 doses of BDP in the preceding month?' (ten doses of BDP in one month are equivalent to 20% of the amount of BDP prescribed for one month). In order to allow comparisons between both methods of measuring compliance, patients were considered compliant within the arbitrary range of 80-120% of the prescribed amount of BDP (18-19). The questionnaire also contained the following questions: 'Did you take BDP at fixed times of the day?' 'Do you think BDP is able to improve the long-term state of the lungs?'

At the end of the four-month period, an assessment of the inhaler technique was carried out by two medical doctors. The scoring system was based on Hilton (12) and consisted of an evaluation of the following four steps, which are considered to be essential for a proper inhalation (and which are also recommended by the instruction manuals accompanying the Rotahaler): 1) initial expiration, 2) upright head position, 3) deep and powerful inspiration, and 4) breath-holding after inspiration. Each step counted for 0, 0.5 or 1 point to the total score of the inhaler technique, in case of incorrect, doubtful or correct performance respectively. A total inhaler score below 2 was judged as 'insufficient', a score between 2 and 3 as 'adequate' and a score above 3 as 'good'. The agreement between both observers of each step of the Rotahaler inhaler technique was corrected for 'chance agreement' by means of the kappa-coefficient (20); when kappa values (range 0.00-1.00) are higher than 0.60, the agreement is judged sufficient to good. Six of the 50 patients used BDP with a pressurized dose inhaler and spacer device because of severe throat complaints. During the study, one patient died because of a myocardial infarction, two stopped with BDP because of severe throat complaints. Therefore the results of 41 patients were analysed in this study.

Analysis
Prior to analysis PC\textsubscript{20} values were log\textsubscript{2} transformed. Individual compliance rates to BDP, measured by counting capsules, were regarded as a continuous variable in the analyses. In order to compare these compliance rates with the presence or absence of compliance to BDP measured by the questionnaire (chi-square test), individual com-
pliance rates were also categorized (<80%, 80-120%, >120%). In all the analyses, the individual compliance rates were related to continuous parameters by means of Pearson's correlations, to ordinal parameters by means of Spearman correlations. Correlates of individual compliance rates to BDP with dichotomous parameters were tested by the unpaired Student's t-test. In asthma and chronic bronchitis separately, relations between the compliance to BDP and the main outcome variables of treatment with BDP (pulmonary symptoms, exacerbations, change in lung function, change in PC_{20}) were investigated by multiple analysis of variance, correcting for initial lung function and compliance to the additional bronchodilator. The Rotahaler inhaler technique was considered as a dichotomous (insufficient/sufficient) or as an ordinal variable (individual inhaler score).

10.3. Results

Compliance with BDP
The mean study period was 118 (range 33 to 158) days. Individual compliance rates with BDP were on average 82 (SD 30)% of the prescribed amount of BDP (range 8-126%). According to our definition of compliance (compliance rate between 80-120%), 19 out of 41 patients (46%) were non-compliant (Figure 10.1). Underuse (less than 80% of the prescribed dose) was far more common than overuse (above

Figure 10.1 Individual compliance rates to BDP (counting capsules): the number of capsules taken, as a percentage of the prescribed dose.
120% of the prescribed dose), in 34 and 12% of the patients respectively (Figure 10.1). However, the questionnaire, which was completed and returned by all patients suggested that only 7% of the patients were non-compliant to BDP. A relationship was found between the individual compliance rates with BDP and the individual compliance rates with the additional bronchodilator (r=0.32, p=0.049). Nevertheless, the average compliance rate to BDP was lower than that for the additional bronchodilator (82%(SD=30)) and 98(SD=29)% respectively, p=0.018). Compliance with BDP was not related to age, sex, diagnosis, inhaler technique, exacerbations or side-effects of BDP. In patients with chronic bronchitis, but not in asthma, compliance with BDP was related to the pulmonary symptoms (r=0.57, p=0.036), the change in FEV$_1$ (r=0.60, p=0.10) and the change in PC$_{20}$ (r=0.72, p=0.031) during steroid treatment. Compliance with BDP was not greater in patients who took their medication at fixed times of the day or who were convinced that BDP is able to improve the long-term state of the lungs (p=0.24 and 0.55, respectively).

**Rotahaler inhaler technique**

There was an acceptable agreement between the two observers on all steps of the Rotahaler inhaler technique, corrected for chance agreement. Kappa was on average 0.63 (range 0.35-1.00). The mean Rotahaler inhaler score was 2.2 (range 0.5-3.5). The Rotahaler inhaler technique was judged 'insufficient' (score of less than 2) in 11 of the 41 patients (27%). Twenty-eight (68%) of the patients had an 'adequate' performance (score 2-3). Only 2 (5%) of the subjects had a 'good' Rotahaler inhaler technique (score 3.5 or 4, Figure 10.2).

*Figure 10.2 Rotahaler inhaler technique. Percentages of patients are given.*

When all steps of the inhaler technique were considered separately (*Table 10.2*), only three of the 41 patients (7%) expired clearly prior to inspiration. Twenty-two (54%) of the subjects did not hold breath after inspiration.
### Table 10.2 Rotahaler inhaler technique, all steps separately. Numbers of patients are given.

<table>
<thead>
<tr>
<th>Step</th>
<th>Not correct</th>
<th>Doubtful</th>
<th>Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressing capsule into hole</td>
<td>0</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Keeping Rotahaler horizontally</td>
<td>16</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Maximal rotation</td>
<td>0</td>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>Initial expiration*</td>
<td>34</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Upward head position*</td>
<td>3</td>
<td>4</td>
<td>34</td>
</tr>
<tr>
<td>Deep and powerful inspiration*</td>
<td>1</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Breath-holding*</td>
<td>22</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Each marked step (#) represents one of the four basic steps of the Rotahaler inhaler technique

### 10.4. Discussion

Most patients asthma and chronic bronchitis are treated in general practice (21). Several studies in the past reported underdiagnosis and undertreatment of asthma in general practice (22-24). Various factors on both doctor and patient level may be responsible for this situation (21,23,25), of which non-compliance is one (21). In the last few years, new evidence for the long-term efficacy of (inhaled) steroids was found (26) whereas doubts emerged about the long-term benefits of continuous bronchodilator therapy, in particular with the beta2-agonists. This has led to the advice that inhaled steroids should be introduced at an early stage (28), which is particularly important for general practice. From this study, it appeared that both non-compliance with inhaled steroids and incorrect inhaler technique are common in the long-term treatment of asthma and chronic bronchitis, even in a controlled trial situation. This stressed the important role of the general practitioner in an adequate prescription of inhaled steroids, regular instruction of inhaler technique and proper information about this prophylactic therapy to patients with asthma and chronic bronchitis.

The mean compliance rate with BDP in this study was 82% of the prescribed dose, a figure comparable with compliance rates to inhaled steroids in two short-term trials (76 and 85% respectively) (7,8). However, individual compliance rates varied from 8 to 126%, with underuse more frequent than overuse. Kruse et al. (29) stated that drug therapy in chronic conditions, even if controlled, is often characterized by a wide range of compliance rates, with underuse predominating. In our study of compliance in asthmatic and chronic bronchitic patients, in whom the likelihood of compliant behaviour (assumed by the GP) was one of the inclusion criteria of the intervention study (15), a comparable pattern was observed. Under uncontrolled and unselected conditions compliance with prescribed drugs in asthma and chronic bronchitis is expected to be much lower (30).

The questionnaire over-estimated compliance to a large extent, when counting capsules was considered as the gold standard. This over-estimation of compliance by asking patients is a well-known phenomenon in clinical practice (18,31). A possible explanation for this result of our study could be that patients did not want to disappoint the investigator after participating in the intervention study for a long period.
We minimized this possibility by asking patients to return the questionnaire anonymously. Another possibility of denying possible non-compliance may be that the assessment of compliance by questionnaire was retrospectively, while capsule counting was prospective. In order to avoid memory bias as much as possible, we only asked for use of medication in the preceding month. Still, counting capsules is known to over-estimate true compliance rates, when compared to even more objective, direct methods such as blood and urine tests (31). This may indicate that the true compliance rates may have been even lower than was found by simply counting capsules.

In general, there are many possible determinants of compliance (32). In this study, we related a number of clinical characteristics but not psychosocial or economic determinants, to compliance. It has been suggested that compliance to steroids should be lower than to bronchodilators, because of the lack of direct symptom-relieving effect of the steroids (9). Indeed, compliance rates to BDP in this study were lower than with bronchodilators. More importantly however, a relationship was observed between the compliance with BDP and the compliance with the additional bronchodilator. In other words, compliance seemed to be patient-dependent rather than drug-dependent. Nevertheless, there is no convincing evidence in literature that patient characteristics (for example age, sex, race, economic status) predict non-compliance to steroids (32). In our study, compliance to BDP was not related to sex, age, and diagnosis.

Compliance with BDP was not related to the patients’ assessment of the ability of the drug to improve the long-term state of the lungs, or to taking BDP at fixed times of the day. With regard to the latter, Haynes found that compliance can be improved by negotiating specific times to take medications (for example during mealtimes) (34). No other studies in which this relation was assessed were found.

It has been proposed that the efficacy of inhaled steroid therapy depends to a large extent on compliance and a proper inhaler technique (9), which was confirmed in two short-term steroid trials (7,8). In the chronic bronchitic patients in this study, the compliance with BDP was related to pulmonary symptoms and the change in lung function and PC20 during steroid treatment. Surprisingly, these relationships were not found in asthma. A possible explanation for this difference may be that in asthma doses between 400 and 800 μg per day already give a maximum treatment effect. Side-effects of steroids may compromise patient compliance (33). In our study, the absence of a relation between compliance to BDP and side-effects of this drug may be caused by the exclusion of six patients who used BDP with a spacer device because of severe throat complaints.

Our cross-sectional assessment showed that one year after extensive inhalation instructions 27% of the patients had an insufficient Rotahaler inhaler technique. In two other reports about the Rotahaler inhaler technique (one in asthmatic children (13) and one in asthmatics of all ages (14), a wrong technique was demonstrated in 56% and 20% of the subjects, respectively. Moreover, it appeared from our study that the majority of patients either did not expire prior to inhalation or did not hold breath after inspiration. Pedersen et al. studied 39 asthmatic children and found that 62% of them did not exhale before a Rotahaler inhalation and 49% of the children did not hold breath for at least seven seconds (13). Although the Rotahaler may be relatively
easy to use, regular instructions of the inhaler technique, with special regard to initial expiration and holding breath afterwards, seem to be essential

We conclude that non-compliance with inhaled steroids and poor inhaler technique often occur in the long-term treatment of asthma and chronic bronchitis, even in a controlled situation. Regular instruction in the inhaler technique and proper information about steroid treatment by the general practitioner is important.

References


11. Treatment of mild asthma and chronic bronchitis with inhaled corticosteroids: is discontinuation of therapy possible?*

Abstract
Inhaled corticosteroids are becoming increasingly important for treatment of asthma and chronic bronchitis in general practice. The aim of this study was to investigate if long term therapy with inhaled corticosteroids could be discontinued in mild asthma and chronic bronchitis when patients are in a clinically stable phase of disease. The study population consisted of 223 patients who entered a two-year randomised controlled bronchodilator intervention study in general practice. The experimental group consisted of 39 patients, who had used inhaled corticosteroids daily during at least the year preceding this study and stopped using these drugs because of participation in the bronchodilator intervention study. The control group consisted of the remaining 184 patients, who had not used corticosteroids in the year preceding the study. At the start of the study, the patients of the two groups were completely comparable with respect to all relevant characteristics. During the study, patients were only treated with a bronchodilator (salbutamol or ipratropium bromide). Outcome measures were exacerbations, symptoms, yearly decline in forced expiratory volume in one second (FEV₁) and yearly change in nonspecific bronchial responsiveness (PC₂₀ histamine). An important outcome measure and also endpoint in this study was the need for additional corticosteroid therapy because of signs and symptoms of increased airway obstruction (advice of responsible GP, insufficient study medication, too severe or too many exacerbations). Treatment with inhaled corticosteroids was discontinued under close observation during an eight week wash-out period just before the start of the trial.

In the experimental group, 22 of the 39 patients (56%) dropped out during the two year study period because of a deterioration of their clinical condition and need for additional (inhaled) corticosteroid treatment. In the control group, only 16 patients dropped out for this reason (9%). This difference was statistically significant (Chi-square=48.5, p<0.0001). In the patients of the experimental group, who could continue without steroids for at least one year, the yearly FEV₁ decline was much larger than in the control subjects.

It was concluded that stopping maintenance treatment with inhaled corticosteroids in patients with mild asthma and chronic bronchitis is troublesome. Instead of stopping or interrupting treatment, GPs are therefore advised to try to find out the minimal effective daily dose of inhaled corticosteroids within each patient which provides adequate control of the disease.

11.1. Introduction

The current understanding that inflammation is a major pathophysiologic mechanism of asthma (1) and maybe also of chronic bronchitis (2), has resulted in a shift in treatment policy towards the early introduction of inhaled corticosteroids (3,4). This tendency is strengthened by the similar finding in two independent studies that continuous therapy with bronchodilators had adverse effects on the control of asthma (5) and

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on the progression of asthma and chronic bronchitis (6). Two retrospective, uncontrolled studies (7,8) and some recent prospective ones (9-11) suggested that (inhaled) corticosteroids can improve the long-term course of asthma or chronic bronchitis. As continuous therapy with bronchodilators may have the opposite effect, treatment with inhaled corticosteroids is probably the only therapy available at the moment which is able to improve the long-term course of asthma and chronic bronchitis.

Since the majority of patients with asthma or chronic bronchitis are treated in general practice (12-13), GPs will have to prescribe this kind of therapy for a growing number of patients. An important question for both GPs and patients is: can treatment with inhaled corticosteroids be interrupted or stopped when patients are in a stable phase of disease? A large proportion of patients in general practice do not really need inhaled steroids for an adequate control of their disease, at least not on a permanent basis. Since inhaled steroids do not have a direct symptom-relieving effect, patient compliance with this medication is a large problem (14). Therefore, patients may ask their GP to stop maintenance treatment with inhaled steroids. Although in general inhaled steroids have relatively mild side-effects, oral candidiasis, hoarseness and irritation of the oropharynx may occur (15,16). Moreover, systemic effects may develop in an increasing number of subjects when doses of 800 μg and over are used (15,16). All these aspects make the above question very relevant.

When corticosteroids ‘cure’ the underlying mechanisms of asthma and chronic bronchitis to some extent, treatment can probably be interrupted. If they only suppress inflammation temporarily, stopping might be difficult. There is very little documented material about the effects of stopping treatment with inhaled corticosteroids.

The aim of this study was to assess the effects of stopping treatment with (inhaled) corticosteroids on the long-term control and progression of asthma and chronic bronchitis in general practice. For this purpose, data of 223 patients with asthma or chronic bronchitis from a large intervention study in general practice were analyzed (6).

### 11.2. Methods

**Patients**

The study population consisted of 223 patients who entered a two-year randomised controlled bronchodilator intervention study in general practice (6,17). The primary goal of this study was to compare the effects of continuous bronchodilator therapy with those of treatment on demand. Patient selection, and in- and exclusion criteria of the intervention study have been described in detail elsewhere (6). In short: 29 GPs were asked to select all their patients aged 30 and over with symptoms of asthma or chronic bronchitis. Only patients with a mild to moderate airway obstruction (FEV₁ or FEV₁/EVC at least two standard deviations below their predicted value (18) but more than 50% of the predicted value) and/or bronchial hyperresponsiveness to histamine (provoking concentration of histamine that produces a 20% fall in FEV₁ (PC₂₀) ≤8mg/ml) were included by the investigators. Exclusion criteria were: depen-
dency on corticosteroids, chronic heart failure, malignant disorders or other life-threatening diseases. The experimental group consisted of 39 patients who had continuously used (inhaled) corticosteroids daily during at least one year preceding the study and had stopped because of participation in the bronchodilator intervention study. Patients had been permitted by their responsible physician to stop corticosteroids, and they entered an eight-week wash-out period before the start of the study during which inhaled corticosteroid treatment (and other pulmonary medication) was stopped. During this period, only inhaled salbutamol or ipratropium bromide were prescribed. When patients had an exacerbation or aggravating symptoms during this period, they were considered to be steroid dependent and therefore excluded from the intervention study. The control group consisted of the remaining 184 patients who had not used (inhaled) corticosteroids in the year preceding the study. Clinical characteristics of the experimental group and the control group are given in Tables 11.1 and 11.2. At the start of the study, there were no significant differences between the two groups. The study was approved by the Medical Ethics Committee of the University of Nijmegen. All patients gave informed consent. The criteria for the diagnosis of asthma or chronic bronchitis were based on the standards of the American Thoracic Society (19). Asthma was defined as the combination of (6,17): 1. reversible obstruction (FEV₁ increased by more than 15% of the baseline value, 60 minutes after the administration of ipratropium bromide 80 μg and salbutamol 400 μg; 2. bronchial hyperresponsiveness to histamine (PC₂₀ ≤8 mg/ml); 3. dyspnoea; 4. allergy and/or wheezing. Chronic bronchitis was defined as the combination of (5,17): 1. chronic cough or chronic sputum production for at least three months during at least two consecutive years; 2. continuous bronchus obstruction (FEV₁ ≤85% of the predicted value).

Table 11.1 Patient characteristics of the 39 patients of the experimental group (continuous use of inhaled corticosteroids during the year preceding the study), and the 184 patients of the control group (no use of corticosteroids during the pre-study period). Standard deviations or ranges are given in brackets. Differences in dichotomous variables are statistically compared by means of the chi-square test, in normally distributed variables by means of the unpaired Student's t-test. No statistically significant differences were present.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>39</td>
<td>184</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>52 (12)</td>
<td>53 (13)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>19/20</td>
<td>107/77</td>
</tr>
<tr>
<td>Symptom score</td>
<td>4.9 (1.7)</td>
<td>4.8 (1.8)</td>
</tr>
<tr>
<td>Pack years</td>
<td>1.4 (12)</td>
<td>1.7 (17)</td>
</tr>
<tr>
<td>Smokers (+/-)</td>
<td>9/15</td>
<td>87/77</td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>7/20</td>
<td>44/123</td>
</tr>
<tr>
<td>FEV₁ %pred</td>
<td>71 (17)</td>
<td>75 (19)</td>
</tr>
<tr>
<td>FEV₁/IVC (%)</td>
<td>62 (15)</td>
<td>63 (14)</td>
</tr>
<tr>
<td>Reversibility FEV₁ (% pred)</td>
<td>14 (10)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>PC₂₀ (mg/ml)##</td>
<td>2.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

# Allergy was defined as at least one positive test out of seven RAST
## geometric mean PC₂₀ is given
Table 11.2 The patient characteristics of the group who participated for at least one year in the two-year randomised controlled study. Standard deviations or ranges are given in brackets. Differences in dichotomous variables are statistically compared by means of the chi-square test, in normally distributed variables by means of the unpaired Student's t-test. No statistically significant differences were present. Patients of the experimental group had used an average daily dose of 450 μg (range 150-800 μg) of an inhaled corticosteroid (budesonide or beclomethasone dipropionate).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Asthma Experimental</th>
<th>Chronic bronchitis Experimental</th>
<th>Asthma Control</th>
<th>Chronic bronchitis Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>10</td>
<td>13</td>
<td>62</td>
<td>99</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 (34-72)</td>
<td>49 (31-68)</td>
<td>50 (27-74)</td>
<td>54 (29-79)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/7</td>
<td>7/6</td>
<td>30/32</td>
<td>62/37</td>
</tr>
<tr>
<td>Pack years (no.)</td>
<td>10</td>
<td>14</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Smokers (+/-)</td>
<td>2/8</td>
<td>72 (23)</td>
<td>27/35</td>
<td>6/7</td>
</tr>
<tr>
<td>Allergy (+/-)#</td>
<td>5/5</td>
<td>2/11</td>
<td>24/37</td>
<td>20/77</td>
</tr>
<tr>
<td>FEVi (%pred)</td>
<td>72 (23)</td>
<td>74 (21)</td>
<td>73 (15)</td>
<td>78 (19)</td>
</tr>
<tr>
<td>PC20 (mg/ml)##</td>
<td>0.9 (0.8)</td>
<td>2.7 (1.9)</td>
<td>17.6 (1.6)</td>
<td>13.5 (1.9)</td>
</tr>
<tr>
<td>Reversibility###</td>
<td>17 (11)</td>
<td>15 (11)</td>
<td>10 (6)</td>
<td>7 (6)</td>
</tr>
</tbody>
</table>

# presence of allergy was defined as at least one positive test out of the 7-RAST tests
## geometric mean PC20 values are given
### reversibility of airway obstruction, measured on the basis of the increase in FEVi and expressed as a percentage of the predicted value

Outcome measures
Under standard bronchodilator treatment the experimental group and the control group were followed during two years. Outcome measures during this period were: the number of exacerbations, severity of symptoms, annual decline in forced expiratory volume in one second (FEVi) and annual change in nonspecific bronchial responsiveness (PC20-histamine). An important outcome measure and also endpoint in this study was the need for additional corticosteroid therapy because of signs and symptoms of increasing airway obstruction (advice of responsible GP, insufficient study medication, too severe or too many exacerbations).

Measurements
• Respiratory symptoms. The severity of respiratory symptoms (cough, phlegm, dyspnoea) was assessed weekly on a scale of 0-4 and recorded in a diary.
• Exacerbations. Exacerbations were defined according to Fletcher et al. (20) with modifications of Boman et al. (21). In case of an exacerbation, a ten-day course of oral prednisone was given: 5-5, 4-4, 3-3, 2-2, 1-1.
• FEVi, PC20-histamine and reversibility of airway obstruction. No bronchodilating medication was taken during at least eight hours before the assessments. Measurements of FEVi were performed with the Microspiro HI-298 (Chest Corporation, Japan) (22) by two qualified laboratory technicians. On all occasions patients had to perform three satisfactory forced vital capacity (FVC) manoeuvres. Data were taken from the curve with the highest sum of FVC and FEVi. Then the bronchial responsiveness to histamine was measured according to the method described by Cockcroft et al. (23), and expressed as the PC20-histamine value (concentration of histamine in
mg/ml producing a 20% fall in FEV1). After the FEV1 had returned to baseline value, the increase in FEV1 60 minutes after the inhalation of both salbutamol 400 μg and ipratropium bromide 80 μg was assessed.

- **Smoking behaviour.** The number of cigarettes per day were recorded by the patients in a weekly report. The smoking history was retrospectively assessed in pack years.

### Treatment during two-year follow-up

All patients were randomly allocated to one of the two parallel treatment regimens:

1. continuous use of salbutamol 400 μg or ipratropium bromide 40 μg, four times daily (dry powder inhalations);
2. use of salbutamol 400 μg or ipratropium 40 μg (dry powder inhalations) on demand (6).

The number of dry powder inhalations used was recorded by the patients in their weekly report. All patients who had used salbutamol during the first year crossed over to ipratropium bromide during the second year and vice versa. The sequence of the drugs was determined by random allocation.

### Analysis

The score of cough, phlegm and dyspnoea was combined in the total symptom score. The annual FEV1 decline was determined by linear regression of FEV1 in the course of time (maximum of 7 measurements). PC20 values were \( \log \) transformed prior to analysis. The annual changes of PC20 were estimated by linear regression of \( \log \text{PC}20 \) in the course of time (maximum of 5 measurements). The influence of stopping treatment with inhaled corticosteroids on the outcome variables was assessed by multiple analysis of variance (MANOVA), controlling for age, sex, height, smoking, pack years, allergy, initial PC20 and FEV1, reversibility of obstruction and treatment regimen (24). The relation between clinical characteristics and the annual FEV1 decline after stopping treatment with steroids in the experimental group was also investigated by means of MANOVA.

### 11.3. Results

In the experimental group, 22 of the 39 patients (56%) dropped out during the two-year study period because of a deterioration of their clinical condition and need for additional (inhaled) corticosteroid treatment (*Figure 11.1*). In the control group, only 16 patients dropped out for the same reason (9%). This difference was significant (Chi-square=48.5, \( p<0.0001 \)) (*Figure 11.1*). Of the 22 dropouts from the experimental group 13 already needed additional corticosteroids during the first six months of the bronchodilator trial.

When the patients who could continue bronchodilator therapy alone during at least one year were analyzed, the following data were found (*Table 11.3*). In asthma, the annual FEV1 decline was larger in the experimental group (165 ml/yr) than in the control group (40 ml/yr) (\( p=0.022, \) *Table 11.3*). No differences between experimental and control group were found with respect to symptoms, exacerbations and the year-
The percentage of patients in the experimental and control group that dropped-out during the two-year study period because of the need for additional corticosteroid therapy.

**Figure 11.1**

<table>
<thead>
<tr>
<th>Patients needing corticosteroids (%)</th>
<th>Experimental group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>

*chi-square = 48.5, p < 0.0001

<table>
<thead>
<tr>
<th></th>
<th>128</th>
</tr>
</thead>
</table>

ly change in PC<sub>20</sub>. For chronic bronchitis, there was no significant difference in the decline in FEV<sub>1</sub> between the experimental group and the control group (95 and 65 ml/yr respectively, *Table 11.3*) or in the other outcome measures.

In the 10 asthmatic patients of the experimental group, it was only allergy that was to some extent related to a larger annual decline in FEV<sub>1</sub> after stopping treatment with corticosteroids (estimate β=131 ml/yr, p=0.114). In the chronic bronchitis patients of the experimental group, less smoking in the past (a lower number of pack years) was significantly associated with a more rapid annual decline in FEV<sub>1</sub> after stopping treatment with corticosteroids (estimate β=7.23 ml/yr, p=0.047).

In the whole group of 72 asthmatic patients, an interaction was observed between stopping treatment with corticosteroids and the reversibility of obstruction at the start of the study (p<0.05). A high reversibility at the start of the study was related to a faster annual FEV<sub>1</sub> decline in the experimental group but to a lower decline in the control group (*Figure 11.2*).
Table 11.3 The effect of stopping treatment with corticosteroids on symptoms, exacerbations, the annual decline in FEV₁ and PC₂₀ in patients with mild asthma and chronic bronchitis. Standard errors of the mean between parentheses. Differences were tested by means of the unpaired Student’s t-test.

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Chronic bronchitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental (n=10)</td>
<td>Control (n=62)</td>
</tr>
<tr>
<td>FEV₁ decline (ml/yr)</td>
<td>165 (50)</td>
<td>40 (20)</td>
</tr>
<tr>
<td>PC₂₀ decline (doubl dose/yr)#</td>
<td>0.33 (0.62)</td>
<td>0.33 (0.22)</td>
</tr>
<tr>
<td>Exacerbations (no /yr)</td>
<td>1 1 (0.3)</td>
<td>0 8 (0.1)</td>
</tr>
<tr>
<td>Symptom score</td>
<td>2 0 (0.5)</td>
<td>2 2 (0.3)</td>
</tr>
</tbody>
</table>

# the annual decline in PC₂₀ is given in doubling doses per year

11.4. Discussion

Long-term treatment with inhaled corticosteroids in asthma and chronic bronchitis is becoming increasingly important for general practice. Two recent guidelines about the therapeutic management of asthma have advocated the early introduction of inhaled corticosteroids in subjects with asthma (3,4). There is increasing evidence for the efficacy of inhaled corticosteroids in patients with chronic bronchitis (11,25), although the effects on average are lower than in asthma. Since most patients with asthma or chronic bronchitis are treated in primary care (12,13) and indications for the use of inhaled corticosteroids are increasing, GPs will have to prescribe this kind of therapy for a growing number of patients.

For GPs an important therapeutic question about treatment with inhaled corticosteroids is if maintenance therapy with these drugs can be discontinued when steroids are not (or no longer) essential for an adequate control of the disease. This question has not been addressed yet in a long-term follow-up study. Therefore, it seemed appropriate to stop steroid therapy under close observation, as we did in this study.

We tried to answer the above question by investigating the progression and control of asthma or chronic bronchitis in 223 patients who were treated in a two-year randomised controlled bronchodilator intervention study in general practice (6). Of the 223 patients 40 had continuously used (inhaled) corticosteroids during the year preceding the intervention study. Only those patients were selected who had mild degrees of airway obstruction (FEV₁ was 75% of the predicted value) and mild symptoms and who -in the opinion of the responsible GP- could stop the use of inhaled corticosteroid therapy. There were no differences in characteristics at the start of the study between the patients who had used inhaled corticosteroids and those who had not. After selection, inhaled corticosteroid treatment was stopped in an eight-week
Figure 11.2 The relationship between the reversibility of obstruction at the start of the study and the annual FEV$_1$ decline in the experimental and control group of asthma. The difference in slopes was statistically compared by means of the unpaired Student's t-test. Regression lines (x=Reversibility (% initial FEV$_1$, y=Change FEV$_1$ (ml/yr):

Regression lines (x=Reversibility (% initial FEV$_1$, y=Change FEV$_1$ (ml/yr):

- Experimental group $y = -2.80x - 90$, $r = 0.52$
- Control group $y = +1.80x - 75$, $r = 0.23$

wash-out period before the start of the study. During this period, we observed whether the symptoms were well controlled by bronchodilators alone and if no exacerbations or signs of increasing airway obstruction developed. If patients did not respond well to this bronchodilating therapy alone, they were excluded from the study.

The present study shows that it is difficult to stop treatment with inhaled corticosteroids in patients with mild asthma and chronic bronchitis. Of the 39 patients 32 needed additional corticosteroids during the two-year period (=56%), a large part of them already during the first six months after stopping. This percentage was much higher than in the control group (only 9%). In the asthmatic patients who were able to continue treatment with bronchodilators alone for at least one year, the annual decline in ventilatory function was much higher than in the control group. In chronic bronchitis, stopping treatment with inhaled corticosteroids was accompanied by an increased annual FEV$_1$ decline in the patients who smoked relatively little (small
number of pack years). It is probable that the patients with a small number of pack years, have less irreversible damage to the airways (26) and therefore respond better to inhaled corticosteroids. As a consequence, stopping treatment with corticosteroids in these patients will also give an increased annual decline in ventilatory function.

The first aim of our randomised controlled study was to compare the effects of continuous bronchodilator therapy with those of treatment on demand on the progression and control of asthma and chronic bronchitis in general practice (6). However, we had a reasonably good design for addressing the question of stopping treatment with inhaled corticosteroids. All patients were closely observed under prospective controlled trial conditions, with a standardized treatment and standardized measurements of symptoms, exacerbations and ventilatory function so that the effects of stopping could be assessed perfectly. Patients who had used inhaled corticosteroids before the start of the study did probably not have a more severe degree of asthma or chronic bronchitis than those who had not. No differences in characteristics were found between the patients of the experimental and control group. In an earlier report, we did not find a relation between the severity of asthma or chronic bronchitis and the use of corticosteroids before the start of the study in the same patient population (27). The use of corticosteroids appeared to be determined by the differences in prescription behaviour of GPs and pulmonary physicians rather than by the severity of the disease (27). The pulmonary physician prescribed almost six times more inhaled steroids than GPs in the same type of patient. We also have data of a few years before the start of the present study about the course of lung function in the patients who were also treated by a pulmonary physician during the pre-study period (and mostly also used inhaled corticosteroids). It appeared that the ventilatory function had hardly deteriorated during the pre-study period. These data suggest that the rapid decline in ventilatory function in the patients of the experimental group must have been caused by stopping treatment with inhaled steroids. The results of this study were not confounded by the bronchodilator intervention, because as all treatment groups were equally represented in the experimental and the control group. Moreover, the bronchodilator treatment was incorporated as a covariate in the multiple analysis of variance (MANOVA) of the annual FEV₁ decline.

The results of this study have several implications for the treatment with inhaled corticosteroids in general practice. It is difficult to interrupt or stop long-term treatment with inhaled corticosteroids because of an increase in the number or severity of exacerbations, an increase in the symptoms of airway obstruction and a rapid fall in ventilatory function. Instead of stopping treatment with inhaled corticosteroids, it might be better to lower the daily dose of inhaled corticosteroids under close monitoring of daily functioning, respiratory symptoms and peakflow rate (3). In this way, the GP can find out the minimal daily dose necessary to provide adequate control of the disease.

The high percentage of patients who needed (additional) corticosteroid therapy and the large decline of FEV₁ in the patients stopping treatment with steroids suggest that inhaled steroids do not cure but only suppress underlying disease processes. It even suggests the existence of a 'rebound increase' in airway inflammation and a consequent excessive increase in airway obstruction after the withdrawal of steroids.
Short-term studies in asthma demonstrated a decline in FEV\textsubscript{1} (28-30) and an increase in nonspecific bronchial responsiveness (31) after withdrawal of inhaled steroids (28,29,31) or dose reduction (30). After stopping treatment with oral steroids or replacement by inhaled corticosteroids, fatal asthma (32) and severe asthma relapse (33) may occur as late as four to eight months after discontinuation. The syndrome of pseudorheumatism (myalgia, arthralgia, joint swelling, etc.) in some asthmatic patients stopping treatment with oral steroids (34) might also suggest a rebound increase in systemic and local inflammatory processes.

In our study, a high reversibility (assessed at the start of the two-year study period) was related to a rapid yearly FEV\textsubscript{1} decline in the asthmatics who stopped treatment with steroids but to a slow yearly decline in the asthmatics of the control group (Figure 11.2). A comparable interaction was found between bronchial hyperresponsiveness and stopping treatment with steroids. This remarkable difference needs clarification. In general, a high reversibility of obstruction is accompanied by a better prognosis (less decline in FEV\textsubscript{1}) (26,35). Therefore, the relation between reversibility and yearly decline in asthmatics who stopped treatment with steroids was the reverse of what was expected. We suggest that a better reversibility (and/or a lower bronchial hyperresponsiveness) in the asthmatics of the experimental group was caused by a higher efficacy of steroids. Stopping treatment with steroids in these asthmatics results in a higher decline in lung function than in the asthmatics with a lower reversibility (or more bronchial hyperresponsiveness). It has been suggested by Josephs et al. that assessments of bronchial hyperresponsiveness in asthma may be of help in the decision to stop corticosteroids (36). However, our study suggests that this is difficult. A less severe degree of bronchial hyperresponsiveness in asthmatics using inhaled corticosteroids might be the consequence of a good response to these drugs. When steroids are discontinued in these patients, a rapid decline in lung function may occur.

We conclude that stopping maintenance treatment with inhaled corticosteroids in patients with mild asthma and chronic bronchitis is not advisable. After discontinuation, about 60% of the patients needed additional inhaled corticosteroids, most of them already during the first six months after stopping. In the patients who could continue without corticosteroids during one or two years, the annual decline in ventilatory function was much larger than in the control subjects. Instead of stopping, GPs are therefore advised to try to find out the minimal effective daily dose of inhaled corticosteroids which provides adequate control of the disease in individual patients.

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Summary

Chapter 1 gives a general introduction and describes the objectives of the studies reported in this thesis. The main study in this thesis is a follow-up to our previously published trial in which the effects of bronchodilators on the course of asthma and COPD was assessed in 223 patients from general practice. This previous trial revealed two important aspects of the treatment of asthma and COPD with bronchodilators alone:

a. A relatively large group of 56 patients had an unexpectedly rapid progression of their asthma or COPD (in terms of annual decline in lung function and frequency of exacerbations).

b. The use of a bronchodilator (salbutamol or ipratropium bromide) four times daily was accompanied by a more rapid annual decline in lung function than treatment on demand;

The main questions of this follow-up study and this thesis are:

1) How can we identify patients with a rapid progression of asthma or COPD?

2) Does treatment with inhaled corticosteroids decelerate this rapid progression of asthma or COPD?

These questions are very much related to the early diagnosis and early treatment of patients with asthma or COPD in general practice. Underdiagnosis and undertreatment of asthma and COPD have been reported in general practice. Most patients with asthma or COPD in the Netherlands and several other countries are treated in general practice, which stresses the importance of the subject.

Simple spirometers for use in general practice are nowadays available. However, the reliability is often unclear. In Chapter 2 the accuracy, precision and linearity of the integrating Microspiro HI-298 flow meter (Chest Corporation, Japan) was assessed by using a Fleisch no. 4 pneumotachograph as a standard. A healthy subject performed forced vital capacity manoeuvres at different levels of lung inflation.

The results showed that the linearity of the Microspiro was good except for the peak expiratory flow rate (PEFR) and the maximal expiratory flow at 25% of the expired volume (MEF75). The random error (measure of precision) of all flow-volume (F-V) indices was lower than 5%. The systematic error (measure of accuracy) was low for the forced expiratory volume in one second (FEV1) and the FVC (1.0% and 4.6% respectively) but much higher for the instantaneous expiratory flows (PEFR 11%; MEF75 7.0%; MEF50 8.5%; MEF25 11.4%). Only the total error in FEV1 complied with the tolerance of 4% of the European Coal and Steel Community (ECSC).
When the measured values were adjusted according to the regression equations of this study, all F-V indices were accurate and precise within 5%. It can be concluded that the portable Microspiro HI-298 is a useful instrument for bedside, work-site spirometry and for use in general practice. As the accuracy of the instantaneous expiratory flows (PEFR, and MEF-values) is moderate, it is advised to adjust these values with the regression equations of this study. The instrument is relatively expensive. For the future, there is (still) a need for cheap but reliable flow-volume meters for use in general practice.

The bronchodilating response (reversibility) after administration of a bronchodilator is not only a useful test for separating asthmatics from patients with COPD, but probably also has prognostic value. Different ways of expressing reversibility are used. It is unclear how reversibility is best expressed. Chapter 3 compares six different ways of expressing the bronchodilating response with respect to: a) the independence of the prebronchodilator FEV₁, and b) the reproducibility of the bronchodilating response. With respect to a), linear regression analysis was applied to the cross-sectional and longitudinal data. With respect to b), coefficients of variation (CV) of the 6 bronchodilating responses during two years of bronchodilator therapy alone were calculated and compared by analysis of variance (ANOVA).

It appeared that no index was independent of the prebronchodilator FEV₁. However, some indices were significantly less dependent on the prebronchodilator lung function and therefore more reproducible than others. The index ‘% initial’ (change as a percentage of the prebronchodilator value) was most dependent on the prebronchodilator lung function and had the worst reproducibility (coefficient of variation ranged from 50-61%). The indices ‘% possible’ (change as a percentage of the predicted minus prebronchodilator value) and ‘% achievable’ (change as a percentage of the maximal postbronchodilator minus prebronchodilator value) were least dependent on the prebronchodilator value and therefore had the highest reproducibility (coefficient of variation ranging from 34-53%).

The way bronchodilating responses should be expressed depends on which index is most informative for the purpose of the test. However, the index ‘% initial’ was most dependent on the prebronchodilator FEV₁ and had the worst reproducibility, whereas for the indices ‘% possible’ or ‘% achievable’ the opposite was found. In bronchodilator studies, the latter expression indices may increase the possibility of detecting changes or differences in bronchodilating efficacy between different drugs. To distinguish between asthmatics and patients with COPD on the basis of reversibility, bronchodilating responses are probably best expressed as ‘% predicted’.

Early detection of patients with an unfavourable course of asthma or COPD in general practice can be important for the prevention of early morbidity and mortality. Chapter 4 deals with the early detection of patients with fast progressive asthma or chronic bronchitis in general practice on the basis of a single cross-sectional assessment of symptoms, smoking behaviour, quality of life, physical signs of the chest, allergy and lung function. 56 Patients showed fast progressive disease (FPD, a rapid annual decline in FEV₁ in combination with a high exacerbation rate). Measurements
at the start of the study were used in a logistic regression analysis in order to detect the patients at risk (those with FPD).

The results showed that a lower maximal expiratory flow at 50% of expired volume (MEF50) was related to an increased risk of FPD in both asthma and chronic bronchitis (relative risks of 16.8 and 8.0 respectively, p<0.05). Most lung function indices, but also quality of life and pack years were significant predictors of FPD in chronic bronchitis (p<0.05). However, with these predictors separately or even with the combination of several relevant clinical variables, it was not possible to detect FPD reliably: 18% of the patients with chronic bronchitis and 22% of those with asthma were still misclassified.

Probably more than one measurement in time (monitoring) is necessary to detect the patients at risk. Monitoring should include assessments of objective ventilatory function indices (PEFR, FEV1 or MEF50).

Chapter 5 studies the hypothesis that the degree of bronchial hyperresponsiveness (BHR) is a risk factor for the progression of airway obstruction in asthma, while in COPD it reflects the existing airway obstruction. The relationships between the (annual change in) PC20-histamine and the (annual change in) FEV1 were investigated in the two-year randomized controlled bronchodilator intervention study. Patients used bronchodilator therapy alone. No steroids were permitted during the study. The results demonstrated that the PC20 at the start of the study was related to the subsequent annual decline of FEV1 in asthma (r=0.32, p<0.05), but not in COPD (r=-0.10, p=0.885). Asthmatic patients with a PC20-value ≤2 mg/ml had an average decline of 118 ml/yr, those with a PC20-value >2 mg/ml of 27 ml/yr. The change of PC20-histamine during the two-year study period was related to the annual change of FEV1 in COPD (r=0.45, p<0.05), but not in asthma (r=0.06, p=0.898). The disturbing influence of possible confounders was investigated and if necessary controlled for (age, sex, height, past and current smoking, allergy, FEV1, bronchodilator response, PC20, exacerbations and the bronchodilator treatment during the study).

BHR as assessed with the PC20-histamine, was involved in the progression of airway obstruction in asthma. In COPD, the degree of BHR only reflected the degree of existing airway obstruction. Therefore, BHR is a ‘cause’ of airway obstruction in asthma, but a ‘consequence’ of airway obstruction in COPD.

An unexpectedly high number of 56 patients with asthma or COPD appeared to have an unfavourable course of their disease during bronchodilator therapy alone. In Chapters 6 and 7, the effects of treatment with inhaled beclomethasone dipropionate (BDP) of 800 μg daily during one and two years respectively on the course of asthma and COPD were assessed.

The results showed that a large initial increase in prebronchodilator FEV1 of +458(SEM 115) ml/yr during the first six months of BDP treatment (p<0.0001) was followed by a decrease of -102(23) ml/yr during months 7-24 in the group as a whole (both asthma and COPD). However, the annual decline in FEV1 during BDP treatment was less than the decline of -160(20) ml/yr before BDP (p<0.05). During the whole treatment period with BDP in asthmatics, the peak expiratory flow rate
(PEFR) significantly improved compared to the value at the start of BDP treatment with a maximal increase of 0.7(0.2) l/s during months 13-15 of BDP treatment (p=0.0006). In patients with COPD, the PEFR increased by 0.21(0.09) l/s compared to the value at the start of steroid treatment during months 4-9 of BDP treatment (p<0.05). Only in asthma, the bronchial hyperresponsiveness (assessed by the provoking concentration of histamine that induces a 20% fall in FEV₁, PC₂₀) improved by BDP treatment. The decrease in PC₂₀ of −0.4 doubling dose/year before BDP was different from the improvement of +1.1 doubling dose/year during BDP treatment (p<0.05). The number of exacerbations decreased during BDP treatment in both asthma and COPD (p<0.05). Besides, beneficial effects of BDP were found on the diurnal variation of the weekly measured PEFR and the severity of symptoms in both asthma and COPD. Only in asthmatics did BDP improve the forced inspiratory volume in one second (FIV₁) and the static lung function indices of residual volume (RV), ratio residual volume/total lung capacity (RV/TLC) and inspiratory vital capacity (IVC).

Additional treatment with BDP of 800 μg daily in the 56 patients with asthma or COPD improved an unfavourable course of disease during bronchodilator therapy alone. This effect was more evident in asthmatics than in patients with COPD.

It is important to identify those patients who will particularly benefit from inhaled corticosteroids, because it will increase our understanding of the effects of steroid action and it may refine the treatment policy of asthma and COPD. Chapter 8 deals with the relationships between the two-year response to inhaled corticosteroids in asthma or COPD and the clinical characteristics at the start of treatment (sex, age, smoking habits, symptoms, quality of life, allergy, static and dynamic spirometry, bronchodilating response, bronchial responsiveness to histamine).

In asthmatics, the average increase in FEV₁ during BDP therapy was larger in patients with a better bronchodilating response (FEV₁-pre: r=0.62, p<0.0001), a higher diurnal peak-flow rate index (FEV₁-post: r=0.42, p<0.05), a severer degree of bronchial hyperresponsiveness (FEV₁-pre: r=−0.64, p=0.066), a higher transfer coefficient (FEV₁-pre: r=−0.76, p<0.01), a larger annual FEV₁ decline during bronchodilator therapy alone (FEV₁-post: r=−0.62, p<0.001) and a lower FIV₁ (FEV₁-post: r=−0.42, p<0.05). It was not possible to predict the improvement in bronchial hyperresponsiveness to BDP from these clinical characteristics. In COPD, the average increase in FEV₁ during BDP treatment was larger in patients with a better bronchodilating response (FEV₁-pre: r=0.89, p<0.0001), a lower FEV₁/IVC (FEV₁-pre: r=−0.54, p<0.05), and a larger decline in FEV₁ during bronchodilator therapy alone (FEV₁-pre: r=−0.77, p<0.0001). No variables were significantly related to the change in postbronchodilator FEV₁ during BDP therapy in COPD.

In asthmatics or patients with COPD, the two-year response in FEV₁ to inhaled BDP 400 μg two times daily was larger in patients with more reversibility, more initial airway obstruction and a larger annual FEV₁ decline during bronchodilator therapy alone. Only in asthmatics was the response to inhaled BDP more pronounced in patients with a larger degree of bronchial hyperresponsiveness, more diurnal variations in peak-flow rate and a higher transfer coefficient.
Improving the quality of life of patients with asthma or COPD is one of the goals of therapy. Chapter 9 describes the effects of BDP on quality of life in asthma or COPD. Quality of life was assessed by means of the Inventory of Subjective Health (ISH) and the Nottingham Health Profile (NHP).

Two-year treatment with BDP did not improve the ISH score or the six dimensions of the NHP, neither in asthma nor in COPD. However, BDP significantly improved the course of lung function (the forced expiratory volume in one second, FEV₁) \( (p<0.0001) \). BDP temporarily decreased respiratory symptoms during the first three months of BDP treatment in asthma \( (p<0.01) \) and during months 7-12 in COPD \( (p<0.05) \). Only a weak cross-sectional and longitudinal correlation was found between (change in) symptoms and quality of life on the one hand and the (change in) FEV₁ on the other.

Although BDP clearly improved the course of lung function and other parameters in asthma and COPD, no improvement in generic quality of life was found in the patients of this study. The data may indicate that patients soon get used to different levels of lung function. In future trials in asthma and COPD, it is advised that both generic and disease-specific health instruments are used and also that quality of life is measured frequently during the early phase of the intervention, e.g. once every month.

The compliance of patients with inhaled corticosteroids and the inhalation technique can be important problems for the long-term effectiveness of this kind of treatment. In Chapter 10 the compliance with and the inhaler technique (dry powder device Rotahaler) of beclomethasone dipropionate (BDP) were investigated. Compliance with BDP was measured by counting capsules single-blind over a four-month period, and also by answering a questionnaire.

The average compliance rate was 82\( (SD\ 30\)% \) of the prescribed amount of BDP. Counting capsules revealed non-compliance with BDP in 46\% of the patients when compliance was defined as using 80 to 120\% of the prescribed amount of BDP. The questionnaire suggested that only 7 \% of the patients was non-compliant. Individual compliance rates were not related to age, sex, type of disease and side-effects of BDP. In chronic bronchitis, but not in asthma, the rates of compliance rates with BDP were related to the pulmonary symptoms, the change in lung function and the change in nonspecific bronchial responsiveness. The inhaler technique was judged insufficient in 27\% of the patients.

Both non-compliance with and a wrong inhaler technique of inhaled steroids often occur in the long-term treatment of asthma and chronic bronchitis, even in a controlled trial situation. This stresses the importance of regular instruction in inhaler technique and proper information about prophylactic steroid treatment by the physician during the treatment of asthma or chronic bronchitis.

An important question to patients with asthma or COPD and their responsible physician is if treatment with inhaled corticosteroids can be discontinued when patients are (again) in a clinically stable phase of their disease. In Chapter 11, the course of mild asthma and COPD after discontinuation of treatment with inhaled corticosteroids was
studied in clinically stable patients. 223 Patients from general practice entered our two-year randomised controlled bronchodilator intervention study. The experimental group consisted of 39 patients, who had used inhaled corticosteroids daily during at least the year preceding this study and had stopped using these drugs because of participation in the bronchodilator intervention study. The subjects were judged as non-steroid-dependent by their physician. Treatment with inhaled corticosteroids was discontinued under close observation during an eight-week wash-out period just before the start of the trial.

The control group consisted of the remaining 184 patients, who had not used corticosteroids in the year preceding the study. At the start of the study, the patients of the two groups were completely comparable with respect to all relevant characteristics.

In the experimental group, 22 of the 39 patients (56%) dropped out during the two-year study period because of a deterioration of their clinical condition and need for additional (inhaled) corticosteroid treatment. In the control group, only 16 patients dropped out for this reason (9%). This difference was statistically significant (Chi-square= 48.5, p<0.0001). In the patients of the experimental group, who could continue without steroids for at least one year, the annual decline in FEV₁ was much larger than in the control subjects.

In general, stopping maintenance treatment with inhaled corticosteroids in patients with mild asthma and chronic bronchitis is not to be recommended. Instead of stopping or interrupting treatment, GPs are therefore advised to try to find out what is the minimal effective daily dose of inhaled corticosteroids within each patient that still provides adequate control of symptoms, exacerbations and lung function.

Conclusions and recommendations

1. The Microspiro HI-298 is a useful instrument for use in general practice. The apparatus complies with the international requirements for spirometry as far as the FEV₁ is concerned. However, it is relatively expensive. There is still a need for cheap but reliable flow-volume meters for use in general practice.

2. The detection in general practice of patients with asthma or COPD at risk (with rapidly progressive disease) is only possible in a reliable way by monitoring the course of disease. Even an extensive cross-sectional assessment of all kinds of relevant characteristics is insufficient to detect the patients at risk. Monitoring of asthma and COPD should imply assessing lung function.

3. The choice of an index to express reversibility depends on which index is most informative for the purpose of the test. However, the most frequently used method of expressing the bronchodilating response as a percentage of the pre-bronchodilator lung function value is most dependent on the prebronchodilator lung function and therefore least reproducible in the course of time.
4. In bronchodilator studies, the use of the expression indices ‘% possible’ (change as a percentage of the predicted minus prebronchodilator lung function value) and ‘% achievable’ (change as a percentage of the maximal postbronchodilator minus prebronchodilator value) increase the possibility of detecting differences in bronchodilating efficacy of different bronchodilator drugs within patients with asthma or COPD. This is the case because these expression indices are least dependent on the prebronchodilator lung function and are most reproducible.

5. Nonspecific bronchial hyperresponsiveness is a ‘cause’ of airflow obstruction in asthma but a ‘consequence’ of airflow obstruction in patients with COPD.

6. Additional treatment with an inhaled corticosteroid (BDP, beclomethasone dipropionate) improves an unfavourable course of asthma or COPD during bronchodilator therapy alone.

7. BDP diminishes symptoms and exacerbations and decelerates the annual decline in lung function in both asthma and COPD. Only in patients with asthma did the inhaled steroid improve bronchial hyperresponsiveness.

8. In both asthma and COPD, the two-year response (in lung function) to inhaled BDP was larger in patients with more reversibility on a bronchodilator, a faster annual decline in lung function during bronchodilator therapy alone and more airway obstruction. Only in asthmatics were more severe bronchial hyperresponsiveness, larger diurnal variations in peak flow and a higher transfer coefficient related to a better two-year response to the inhaled steroid.

9. No influence of two-year treatment with inhaled BDP was found on quality of life in asthma and COPD as assessed by the generic quality of life instruments ‘Inventory of Subjective Health (ISH)’ or the ‘Nottingham Health Profile (NHP)’. As patients may get rapidly used to different levels of lung function, the quality of life should be measured frequently during the early phase of the intervention (e.g. once every month). In future trials in asthma and COPD, it is advised that both generic and disease-specific health instruments are used.

10. Both patient compliance with and inhaler technique of corticosteroids are a problem for the long-term treatment of asthma and COPD with this type of drugs. Regular instruction in inhaler technique and proper information about prophylactic steroid treatment by the physician during the treatment of asthma or chronic bronchitis may improve these aspects of treatment.

11. Stopping maintenance treatment with inhaled corticosteroids in patients with mild to moderate asthma or chronic bronchitis is not to be recommended. Instead of stopping or interrupting treatment, GPs are therefore advised to try to find out what is the minimal effective daily dose of inhaled corticosteroids within each patient that still provides adequate control of the disease.
Samenvatting

Hoofdstuk I geeft een algemene introductie en beschrijft de onderzoeksvragen van de studies in dit proefschrift. De meeste patiënten met astma en COPD in Nederland en verschillende andere landen worden in de eerste lijn behandeld. Er zijn regelmatig publikaties verschenen over onderdiagnostiek en onderbehandeling van astma en COPD in de huisartsenpraktijk. De hoofdstudie in dit proefschrift is een vervolg op ons reeds eerder gepubliceerde onderzoek waarin de effecten van bronchusverwijders op het beloop van astma en COPD werden onderzocht bij 223 patiënten uit de huisartsenpraktijk. Dit onderzoek liet twee belangrijke aspecten van de behandeling van astma en COPD met alleen bronchusverwijders zien:

a. Bij een relatief grote groep van 56 patiënten met astma of COPD trad een onverwacht snelle progressie op in hun ziekte (in termen van jaarlijkse longfunctiedaling en frequentie van exacerbaties).

b. Het gebruik van een bronchusverwijder (salbutamol of ipratropium bromide) vier maal daags ging gepaard met een snellere daling in longfunctie dan het ‘zo nodig’ gebruik;

De hoofddoelen van deze vervolgstudie en van dit proefschrift zijn:

1) Hoe kunnen patiënten met een snelle progressie van astma of COPD worden opgespoord?

2) Kan behandeling met inhalatiecorticosteroïden deze snelle progressie van astma of COPD afremmen?

Deze onderzoeksvragen zijn sterk gerelateerd aan de vroege opsporing en behandeling van patiënten met astma en COPD in de huisartsenpraktijk.

Eenvoudige spirometers voor gebruik in de huisartsenpraktijk zijn tegenwoordig voorhanden. De betrouwbaarheid van deze instrumenten is echter vaak onduidelijk. In hoofdstuk 2 werden de nauwkeurigheid, de zuiverheid en de lineariteit van de flow-volume meter Microspiro HI-298 (Chest Corporation, Japan) onderzocht door een Fleisch no. 4 pneumotachograaf als standaard te gebruiken. Een gezonde proefpersoon voerde geforceerde expiraties uit bij verschillende longinflatie niveaus.

De resultaten lieten zien dat de lineariteit van de Microspiro goed was behalve voor de peakflowwaarde (PEFR) en de maximale expiratoire flow bij 25% van het geëxpireerde volume (MEF75). De toevallige fout (maat voor de zuiverheid) van alle flow-volume (F-V) parameters was lager dan 5%. De systematische fout (maat voor de nauwkeurigheid) was laag voor het geforceerde expiratoire volume in één seconde (FEV1) en de geforceerde vitale capaciteit (FVC) (respectievelijk 1,0% en 4,6%).
maar veel groter voor de direct gemeten expiratoire flows (PEFR 11,0%; MEF75 7,0%; MEF50 8,5%; MEF25 11,4%). Alleen de totale fout in de FEV1 voldeed aan het tolerantiecriterium van 4% van de Europese Gemeenschap voor Kolen en Staal (EGKS). Wanneer de gemeten waarden werden aangepast volgens de regressie- vergelijkingen in deze studie waren alle F-V indices tot op 5% nauwkeurig en zuiver.

De conclusie was dat de draagbare Microspiro HI-298 een geschikt instrument is voor spirometrie aan het bed, op de werkplek en voor gebruik in de huisartsenpraktijk. Aangezien de nauwkeurigheid van de direct gemeten expiratoire flows (PEFR, en MEF-waarden) matig is, is het aan te bevelen om deze waarden aan te passen volgens de regressievergelijkingen in deze studie. Het instrument is relatief duur. In de toekomst is er behoefte aan goedkopere maar betrouwbare flow-volume meters voor gebruik in de huisartsenpraktijk.

De directe reactie na toediening van een bronchusverwijder (reversibiliteit) is niet alleen van belang om een onderscheid te kunnen maken tussen patiënten met astma of COPD maar heeft tevens prognostische betekenis. Er zijn verschillende methoden in gebruik om de reversibiliteit uit te drukken. Het is onduidelijk welke methode het beste is. In hoofdstuk 3 worden zes verschillende methoden om de bronchusverwijden-de reactie uit te drukken vergeleken met betrekking tot: a) de mate van onafhankelijkheid van de FEV1 waarde vóór bronchusverwijding (prebronchodilatoire FEV1), en b) de reproduceerbaarheid van de directe reactie op bronchusverwijders. Met betrekking tot a), werd lineaire regressieanalyse toegepast op de cross-sectionele en de longitudinale waarden. Met betrekking tot b), werden de variatiecoëfficiënten (VC) van de zes bronchodilatoire reacties gedurende de twee-jarige behandeling met alleen bronchusverwijders berekend en vergeleken met behulp van variantieanalyse (ANOVA).

De resultaten gaven aan dat geen enkele uitdrukkingsmethode onafhankelijk was van de prebronchodilatoire FEV1. Echter, sommige indices waren significant minder afhankelijk van de prebronchodilatoire longfunctie en daardoor meer reproduceerbaar dan anderen. De index ‘% initial’ (toename als percentage van de FEV1 waarde vóór bronchusverwijding) was het meest afhankelijk van de prebronchodilatoire longfunctie en had de slechtste reproduceerbaarheid (de variatiecoëfficiënten varieerden van 50-61%). De indices ‘% possible’ (toename als percentage van de voorspelde minus de prebronchodilatoire waarde) en ‘% achievable’ (toename als percentage van de maximale postbronchodilatoire minus prebronchodilatoire waarde) waren het minst afhankelijk van de prebronchodilatoire waarden en hadden daarom de hoogste reproduceerbaarheid (de variatiecoëfficiënten varieerden van 34-53%).

De manier waarop de directe reactie op een bronchusverwijder moet worden uitgedrukt hangt af van de vraag welke methode de meeste informatie geeft over het doel van de test. De index ‘% initial’ was het meest afhankelijk van de prebronchodilatoire FEV1 en had de slechtste reproduceerbaarheid, terwijl voor de indices ‘% possible’ en ‘% achievable’ het omgekeerde gevonden werd. In onderzoeken naar de directe reactie op bronchusverwijders kunnen de laatste uitdrukkingsmethoden de mogelijkheid vergroten om veranderingen of verschillen in directe reacties tussen verschillende bronchusverwijders op te sporen. Voor het onderscheid tussen patiënten
met astma en COPD op basis van de reactie op bronchusverwijders kan deze waar­
schijnlijk het best uitgedrukt worden als ‘% predicted’.

Vroege opsporing van patiënten met ongunstig beloop van astma of COPD in de
huisartsenpraktijk is van belang voor de preventie van vroege morbiditeit en mortalitei­
it. In hoofdstuk 4 wordt onderzocht of een vroege opsporing van patiënten met een
snel progressieve vorm van astma of chronische bronchitis mogelijk is in de huisart­
senpraktijk aan de hand van een eenmalige cross-sectionele meting van symptomen,
rookgedrag, fysische diagnostiek, allergie en longfunctie. Van de 162 patiënten had­
den er 56 een snel progressieve ziekte (FPD (fast progressive disease), een snelle
longfunctiedaling in combinatie met een hoog aantal exacerbaties). Metingen aan het
begin van het onderzoek werden in een logistische regressieanalyse gebruikt voor het
opsporen van de risicopatiënten (met een snel progressieve vorm van astma of chro­
nische bronchitis).

Uit het onderzoek bleek dat een lagere maximale expiratoire flow bij 50% van het
geëxpireerde volume (MEF50) gerelateerd was aan een toegenomen risico op FPD
zowel bij astma als bij chronische bronchitis (relatieve risico’s van respectievelijk
16,8 and 8,0, p<0,05). Niet alleen de meeste longfunctieparameters maar ook kwalitei­
t van het leven en pack years waren significante voorspellers van FPD bij chroni­
sche bronchitis (p<0,05). Echter, met deze voorspellers afzonderlijk of zelfs met de
combinatie van verschillende, klinisch relevante parameters was het niet mogelijk
om op een individueel niveau FPD op betrouwbare wijze te voorspellen: 18% van de
patiënten met chronische bronchitis en 22% van de patiënten met astma werden nog
verkeerd ingedeeld.

Meer dan één meting (monitoring) van o.a. longfunctie is nodig om risicopatiën­
ten betrouwbaar op te sporen.

Hoofdstuk 5 bestudeert de hypothese dat bij patiënten met astma de bronchiale hyper­
reactiviteit (BHR) een risicofactor is voor de progressie van luchtwegobstructie ter­
wijl bij patiënten met COPD de mate van BHR vooral bepaald wordt door de ernst
van de chronische luchtwegobstructie. De relaties tussen de (jaarlijkse verandering
in) PC20-histamine en de (jaarlijkse verandering in) FEV1 werden onderzocht in het
twee jaar durende gerandomiseerde en gecontroleerde interventieonderzoek met
bronchusverwijders. Het gebruik van steroiden tijdens het onderzoek was niet toege­
staan (behalve tijdens exacerbaties).

De resultaten lieten zien dat de PC20 aan het begin van het onderzoek gerelateerd
was aan de daaropvolgende jaarlijkse daling in FEV1 bij astma (r=0,32, p<0,05) maar
niet in COPD (r=-0,10, p=0,885). Bij astmapatiënten met een PC20-waarde ≤2 mg/ml
was de gemiddelde daling 118 ml/jaar, bij astmatici met een PC20-waarde >2 mg/ml
27 ml/jaar. De verandering in PC20-histamine gedurende de twee jaar durende onder­
zoekspériode was gerelateerd aan de jaarlijkse verandering in FEV1 bij patiënten met
COPD (r= 0,45, p<0,05), maar niet in astma (r= 0,06, p= 0,898). De invloed van mo­
gelijke storende variabelen werd onderzocht en zo nodig werd hiervoor gecorrigeerd
(leeftijd, geslacht, lengte, rookgedrag vroeger en nu, allergie, FEV1, reversibiliteit,
PC20, exacerbaties en het type bronchusverwijdende therapie tijdens de studie).
BHR gemeten met de histamine provocatietest, is een risicofactor voor de progressie van luchtwegobstructie bij patiënten met astma. Bij patiënten met COPD gaf de mate van BHR voornamelijk de ernst van de reeds bestaande luchtwegobstructie aan. BHR is daarmee een ‘oorzaak’ van luchtwegobstructie bij astma, maar een ‘gevolg’ van luchtwegobstructie bij COPD.

Een onverwacht groot aantal van 56 patiënten met astma of COPD bleek gedurende behandeling met alleen bronchusverwijzers een ongunstig ziektebeloop te vertonen. In de hoofdstukken 6 en 7 wordt onderzocht of deze snelle progressie van astma of COPD vertraagd kan worden door aanvullende behandeling met een inhalatiecorticosteroïd (BDP, beclometason dipropionaat) in een dosering van 800 μg per dag gedurende respectievelijk één en twee jaar.

De resultaten lieten zien dat een grote initiële stijging van de prebronchodilatoire FEVi van +458(SEM 115) ml/jaar gedurende de eerste zes maanden van de behandeling met BDP (p<0,0001) gevolgd werd door een afname van −102(23) ml/jaar gedurende de maanden 7-24 in de groep als geheel (zowel astma als COPD). Echter, de jaarlijkse daling in FEVi gedurende het gebruik van BDP was minder dan de daling van −160(20) ml/jaar voor het gebruik van BDP (p<0,05). Gedurende de gehele behandelingperiode met BDP bij patiënten met astma was de peakflowwaarde (PEFR) significant toegenomen in vergelijking met de waarde aan het begin van de BDP behandeling. De maximale toename was 0,7(0,2) l/s, welke gedurende de maanden 13-15 van de BDP behandeling optrad (p=0,0006). Bij patiënten met COPD nam de PEFR toe met 0,2(0,1) l/s gedurende de maanden 4-9 van de behandeling met BDP in vergelijking met de waarde aan het begin van de behandeling met steroiden (p<0,05). De bronchiale hyperreactiviteit (gemeten aan de hand van de histamineconcentratie die een 20% daling van de FEVi geeft, de PC20) verbeterde alleen bij patiënten met astma. De afname in PC20 van −0,4 verdubbelingsdoserin jaar voor het gebruik van BDP verschilde van de verbetering van +1,1 verdubbelingsdoserin jaar gedurende het gebruik van BDP (p<0,05). Het aantal exacerbaties verminderde gedurende BDP behandeling bij zowel astma als COPD (p<0,05). Daarnaast werden gunstige effecten van BDP gevonden op de variaties in de wekelijks gemeten PEFR over de dag en de ernst van de symptomen in zowel astma als COPD. Alleen bij astmapatiënten verbleerde BDP het maximaal geïnspireerde volume in één seconde (FIV1) en de statische longfunctieindices residuaal volume (RV), ratio residuaal volume/totale long capaciteit (RV/TLC) and inspiratoire vitale capaciteit (IVC).

Additionele behandeling met BDP in een dosering van 800 μg per dag bij de 56 patiënten met astma of COPD in deze studie verbeterde het ongunstige beloop van de ziekte gedurende behandeling met alleen bronchusverwijzers. Dit effect was duidelijker aanwezig bij patiënten met astma dan bij COPD.

Het is belangrijk om patiënten te kunnen identificeren die met name op een inhalatiecorticosteroïd zullen reageren, omdat het ons inzicht in de effecten van steroiden kan vergroten en mogelijk het behandelingseleven ten aanzien van astma of COPD kan nuanceren. In hoofdstuk 8 worden de relaties tussen de effecten van behandeling met een inhalatiecorticosteroïd (BDP) gedurende twee jaar en de klinische karakteristie-
ken aan het begin van de behandeling (geslacht, leeftijd, rookgedrag, symptomen, kwaliteit van leven, allergie, statistische en dynamische spirometrie, directe reactie op bronchusverwijders, bronchiale hyperreactiviteit) bij patiënten met astma of COPD onderzocht.

De gemiddelde toename in FEV₁ gedurende het gebruik van BDP bij astma was groter bij patiënten met een grotere directe reactie op bronchusverwijders (FEV₁-pre: \( r=0,62, p<0,0001 \)), een hogere diurnale PEFR index (FEV₁-post: \( r=0,42, p<0,05 \)), een grotere bronchiale hyperreactiviteit (FEV₁-pre: \( r=-0,64, p=0,066 \)), een hogere transfer coëfficiënt (FEV₁-pre: \( r=0,76, p<0,01 \)), een grotere jaarlijkse FEV₁ daling gedurende monotherapie met bronchusverwijders (FEV₁-post: \( r=-0,62, p<0,001 \)) en een lagere FIV₁ (FEV₁-post: \( r=-0,42, p<0,05 \)). Het was niet mogelijk om de verbetering in bronchiale hyperreactiviteit gedurende BDP behandeling te voorspellen vanuit deze afzonderlijke klinische karakteristieken. Bij COPD was de gemiddelde toename in FEV₁ groter bij patiënten met een grotere directe reactie op bronchusverwijders (FEV₁-pre: \( r=0,89, p<0,0001 \)), een lagere FEV₁/FVC (FEV₁-pre: \( r=-0,54, p<0,05 \)), en een grotere daling in FEV₁ gedurende monotherapie met bronchusverwijders (FEV₁-pre: \( r=-0,77, p<0,0001 \)). Geen enkele variabele was significant gerelateerd aan de verandering in postbronchodilatoire FEV₁ gedurende BDP gebruik bij COPD.

De effecten op de FEV₁ door behandeling met geïnhaaleerd BDP gedurende twee jaar bij patiënten met astma of COPD is groter bij patiënten met meer reversibiliteit, meer initiële luchtwegobstructie en een grotere longfunctiedaling gedurende behandeling met alleen bronchusverwijders. Alleen bij patiënten met astma was de reactie op geïnhaaleerd BDP ook meer uitgesproken bij patiënten met meer bronchiale hyperreactiviteit, een hogere diurnale PEFR index en een grotere transfer coëfficiënt.

Verbetering van kwaliteit van leven bij patiënten met astma of COPD is onder meer één van de doelen van therapie. Hoofdstuk 9 beschrijft de effecten van BDP op de kwaliteit van het leven bij patiënten met astma of COPD. De kwaliteit van het leven werd gemeten aan de hand van de Inventory of Subjective Health (ISH) en de Nottingham Health Profile (NHP).

De twee jaar durende behandeling met BDP verbeterde de ISH score of de score van de zes dimensies van de NHP niet, noch bij astma, noch bij COPD. Echter, BDP verbeterde het beloop van longfunctie (het geforceerde expiratoire volume in één seconde, de FEV₁) significant (p<0,0001). BDP verminderde de ernst van de symptomen tijdelijk gedurende de eerste drie maanden van de BDP behandeling bij astma (p<0,01) en gedurende de maanden 7-12 bij COPD (p<0,05). Er werd zowel cross-sectioneel als longitudinaal slechts een zwakke correlatie gevonden tussen de (verandering in) symptomen en kwaliteit van het leven aan de ene kant en de (verandering in) FEV₁ aan de andere kant.

Hoewel BDP duidelijk het beloop van longfunctie en andere parameters bij astma en COPD verbeterde, werd geen verbetering in kwaliteit van het leven gevonden bij de patiënten in deze studie. Deze gegevens kunnen er op wijzen dat patiënten snel wennen aan wisselende longfunctieniveaus. In toekomstige onderzoeken naar astma en COPD wordt aangeraden dat zowel algemene als ziektespecifieke kwaliteit-van-leven instrumenten worden gebruikt en tevens dat kwaliteit van het leven frequent
gemeten wordt gedurende de vroege fase van de interventie, bijv. één keer per maand.

De therapietrouw van patiënten voor inhalatiecorticosteroïden en de inhalatietechniek kunnen een probleem zijn voor de effectiviteit van een lange-termijns behandeling met deze middelen. *Hoofdstuk 10* onderzoekt de therapietrouw (compliantie) voor en de inhalatietechniek (droge poeder inhalator Rotahaler) van beclometason dipropionaat (BDP). De therapietrouw voor BDP werd gemeten door het tellen van capsules over een periode van vier maanden en door het invullen van een vragenlijst.

Het gemiddelde gebruik bedroeg 82 (SD 30)% van de voorgeschreven hoeveelheid BDP. Het tellen van capsules toonde non-compliantie aan bij 46% van de patiënten wanneer compliantie werd gedefinieerd als het gebruik van 80 tot 120% van de voorgeschreven dosis van BDP. De vragenlijst suggereerde non-compliantie bij slechts 7% van de patiënten. De individuele compliantieratio's waren niet gerelateerd aan leeftijd, geslacht, diagnose en bijwerkingen van BDP. De therapietrouw voor BDP was wel gerelateerd aan een beter beloop van symptomen, longfunctie en bronchiale hyperreactiviteit gedurende BDP gebruik bij patiënten met chronische bronchitis maar niet bij patiënten met astma. De inhalatietechniek werd bij 27% van de patiënten als onvoldoende beoordeeld.

Zowel non-compliantie voor als een verkeerde inhalatietechniek van inhalatiecorticosteroïden kunnen vaak voorkomen gedurende de lange-termijns behandeling van astma en chronische bronchitis, zelfs in gecontroleerde onderzoeksomstandigheden. Dit benadrukt het belang van regelmatige instructie van de inhalatietechniek en duidelijke informatie over de profylactische behandeling met steroidalen door de behandelend arts gedurende de behandeling van patiënten met astma en chronische bronchitis.

Een belangrijke vraag voor patiënten met astma of COPD en hun behandelend arts is of behandeling met inhalatiecorticosteroïden gestopt kan worden wanneer patiënten weer in een klinisch stabiele toestand zijn. In *hoofdstuk 11* werd het beloop van een milde vorm van astma en COPD bestudeerd bij klinisch stabiele patiënten, nadat de behandeling met inhalatiecorticosteroïden was gestopt. De onderzoekspopulatie was samengesteld uit 223 patiënten die meededen aan ons gerandomiseerd, gecontroleerd interventieonderzoek in de huisartsenpraktijk. De **experimentele groep** bestond uit 39 patiënten die dagelijks inhalatiesteroïden hadden gebruikt gedurende het jaar vóór het onderzoek en die stopten met het gebruik hiervan vanwege deelname aan het interventieonderzoek met bronchusverwijders. De mensen werden als niet-steroidafhankelijk beoordeeld door hun behandelend arts. De behandeling met inhalatiecorticosteroïden werd gestopt onder nauwlettende observatie gedurende een acht weken durende wash-out periode net voor aanvang van het onderzoek. De **controlegroep** bestond uit de andere 184 patiënten die geen inhalatiecorticosteroïden hadden gebruikt in het jaar voorafgaande aan de studie. Aan het begin van de studie waren de patiënten van de twee groepen wat betreft alle relevante kenmerken volledig vergelijkbaar.

In de experimentele groep vielen 22 van de 39 patiënten uit gedurende de twee jaar durende onderzoekspériode (=56%) vanwege een verslechtering van hun klinische toestand en de behoefte aan (inhalatie)corticosteroïden. In de controlegroep vie-
len slechts 16 patiënten om deze reden uit (=9%). Dit verschil was statistisch signifi-
cant (Chi-kwadraat= 48,5, p<0,0001). Bij de patiënten van de experimentele groep
die tenminste een jaar zonder inhalatiecorticosteroiden konden was de jaarlijkse da-
ing in FEV₁ veel groter dan bij de personen uit de controlegroep.

In het algemeen is het stoppen van de onderhoudsbehandeling met inhalatiecorti-
costeroiden bij patiënten met een milde vorm van astma en chronische bronchitis niet
aan te bevelen. In plaats van de behandeling te stoppen of te onderbreken wordt ge-
adviseerd om de minimale effectieve dosis inhalatiecorticosteroiden uit te vinden die
nog een goede controle van symptomen, exacerbaties en longfunctie geeft bij elke in-
dividuele patiënt.

Conclusies en aanbevelingen

1. De Microspiro HI-298 is een geschikt instrument voor gebruik in de huisartsen-
praktijk. Het apparaat voldoet aan de internationale criteria voor spirometrie
voor zover het de FEV₁ betreft. Het is echter relatief duur. Er is nog steeds be-
hoefte aan goedkope maar betrouwbare flow-volume meters voor gebruik in de
huisartsenpraktijk.

2. De opsporing van patiënten met snel progressief astma of COPD in de huisart-
senpraktijk is alleen op een betrouwbare manier mogelijk door monitoring van
het ziektebeloop, m.n. door het meten van longfunctie. Zelfs een uitgebreide
cross-sectionele meting van allerlei klinisch relevante karakteristieken is onvol-
doende om de risico-patiënten op te sporen.

3. De meest gebruikte methode om de directe reactie op bronchusverwijders als een
percentage van de waarde voor bronchusverwijding (prebronchodilatoire long-
functiewaarde) uit te drukken is het meest afhankelijk van deze prebronchodila-
toaire longfunctie en daarom het minst reproduceerbaar in de loop van de tijd.

4. In onderzoeken naar de directe reacties op bronchusverwijders kan het gebruik
van de uitdrukkingsmethoden '%possible' (toename als percentage van de voor-
spelde minus de prebronchodilatoire waarde) en '% achievable' (toename als
percentage van de maximale postbronchodilatoire minus de prebronchodilatoire
waarde) bij patiënten met astma of COPD de mogelijkheid vergroten om ver-
schillen in directe reacties tussen verschillende bronchusverwijders aan te tonen.

5. Niet-specifieke bronchiale hyperreactiviteit is een 'oorzaak' van luchtwegob-
structie bij astma maar een 'gevolg' van luchtwegobstructie bij patiënten met
COPD.

6. Additionele behandeling met een inhalatiecorticosteroïd (BDP, beclometason di-
propionaat) verbetert een ongunstig beloop van astma en COPD gedurende be-
handeling met alleen bronchusverwijders.
7. BDP vermindert de ernst van symptomen, de frequentie en duur van exacerbaties en vertraagt de jaarlijkse longfunctiedaling bij patiënten met astma of COPD. De bronchiale hyperreactiviteit verbetert alleen bij patiënten met astma.

8. Zowel bij patiënten met astma als bij COPD zijn de tweejarige effecten (in longfunctie) gedurende behandeling met BDP groter bij patiënten met meer reversibiliteit, een snellere daling in longfunctie gedurende behandeling met alleen bronchusverwijzers en meer luchtwegobstructie. Alleen bij astma gaan meer bronchiale hyperreactiviteit, een grotere diurnale PEFR index en een hogere transfercoëfficiënt gepaard met grotere effecten van het inhalatiesteroïd.

9. De twee jaar durende behandeling met BDP had geen invloed op kwaliteit van het leven bij astma en COPD gemeten aan de hand van de algemene kwaliteit van leven instrumenten ‘Inventory of Subjective Health (ISH)’ en de ‘Nottingham Health Profile (NHP)’. Aangezien patiënten mogelijk snel wennen aan een ander longfunctieniveau, verdient het aanbeveling dat kwaliteit van het leven voldoende vaak gemeten wordt gedurende de eerste fase van de interventie (bijvoorbeeld eens per maand). In toekomstige onderzoeken naar astma en COPD wordt geadviseerd om zowel algemene alsook ziekte-specifieke instrumenten te gebruiken.

10. Zowel de therapietrouw van patiënten voor inhalatiecorticosteroïden als de inhalatietechniek vormen een probleem voor de lange-termijns behandeling van astma en COPD met dit type medicijn. Regelmatige instructie van de inhalatietechniek en duidelijke informatie over de achtergronden van profylactische behandeling met steroïden door de behandelend arts kunnen mogelijk tot verbetering leiden.

11. In het algemeen is het stoppen van een onderhoudsbehandeling met inhalatiecorticosteroïden bij patiënten met een milde vorm van astma of chronische bronchitis niet aan te bevelen. In plaats van de behandeling met inhalatiecorticosteroïden te stoppen of te onderbreken kunnen artsen beter proberen de minimale effectieve dosis te vinden die nog een goede controle van symptomen, exacerbaties en longfunctie geeft.
Appendix. The calculation of the effect of regression-to-the-mean in the BDP trial

For the BDP trial, 56 out of 160 patients with asthma or COPD were selected on the basis of a relatively fast annual decline in lung function. Because of this selection, some degree of spontaneous improvement (on the basis of regression-to-the-mean) can be expected in the subsequent two-year period of treatment with BDP, which is not really attributable to BDP. In this way, regression-to-the-mean can introduce bias in the BDP trial by overestimating the effect of BDP. Therefore, an important question is how large the disturbing influence of regression-to-the-mean is. It is probably small because regression-to-the-mean mainly plays a part with one measurement and decreases rapidly with two or more assessments (1). The main outcome measure of the BDP trial was the annual decline in FEV1, which was estimated by seven measurements of the FEV1 during a period of two years. A quantification of the effect of regression-to-the-mean is possible by using the statistical models of Gardner et al., Das et al., and Davis (1-3).

Let a continuous random variable $X$ be measured twice on the subjects of a population. Both measurements $X_1$ and $X_2$ are assumed to be normally distributed in the stationary population of subjects with the same $\mu$, the same variance $\sigma^2$ and correlation coefficient $r$ ($0 < r < 1$) due to within-subject error. The mathematical expectation of the difference $X_1 - X_2$, given $X_1 = x$, then becomes:

$$E(X_1 - X_2 | X_1 = x) = (1-r) \cdot (x - \mu) = R(x) \text{ in which } R(x) \text{ is the regression-to-the-mean effect of } x.$$  

The correlation coefficient $r$ of $X_1$ and $X_2$ equals the proportion of the total variance $\sigma^2$ of $X$ attributable to the between-patient variance:

$$r = \frac{\delta^2}{\sigma^2} \text{ in which } \delta^2 \text{ is the variance due to within-patient error.}$$  

In our situation, the annual decline in FEV1 appeared to be a normally distributed variable with a mean $\mu$ of 56.9 ml/yr and a standard deviation $\sigma$ of 150.7 ml/yr. The regression-to-the-mean effect of a patient $i$, selected for steroid treatment with an annual decline in FEV1 of $x_i$, is given by $R(x_i) = (1-r) \cdot (x_i - \mu)$. The average regression-to-the-mean $R(x)$ in the whole population of $n$ patients selected for steroid treatment is given by:

$$R(x) = \frac{1}{n} \sum_{i=1}^{n} R(x_i)$$

The $r$ in our study was

$$r = \frac{(150.7)^2 - (93.2)^2}{(150.7)^2} = 0.72$$

We calculated the treatment effect of BDP during the first six months before and after adjusting for the effect of regression-to-the-mean. The following data were found:
Treatment effect during the first six months of BDP treatment

<table>
<thead>
<tr>
<th>Disease</th>
<th>Before adjusting</th>
<th>After adjusting</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change FEV₁ (ml/yr)</td>
<td>Change FEV₁ (ml/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>+562 (148)</td>
<td>+530 (150)</td>
<td>0.0002</td>
<td>0.003</td>
</tr>
<tr>
<td>COPD</td>
<td>+323 (183)</td>
<td>+299 (191)</td>
<td>0.041</td>
<td>0.049</td>
</tr>
</tbody>
</table>

The treatment effect and the corresponding p-values hardly changed when the values were adjusted for regression-to-the-mean. A significant treatment effect remained in both asthma and COPD.

We made a comparable analysis for the effect of BDP during two years. We calculated the gain in FEV₁ caused by two-year additional treatment with BDP. This was done by comparing the end-point of FEV₁ after the two-year treatment with BDP with the extrapolated end-point when bronchodilator therapy alone had been continued during the third and fourth year. The gain in FEV₁ was calculated before and after adjusting for the influence of regression-to-the-mean.

**Gain in FEV₁ after two-year BDP therapy**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Before adjusting</th>
<th>After adjusting</th>
<th>p-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gain in FEV₁ (l)</td>
<td>Gain in FEV₁ (l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>+0.34 (0.08)</td>
<td>+0.28 (0.05)</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asthma</td>
<td>+0.42 (0.08)</td>
<td>+0.36 (0.08)</td>
<td>0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>COPD</td>
<td>+0.25 (0.13)</td>
<td>+0.20 (0.11)</td>
<td>0.073</td>
<td>0.096</td>
</tr>
</tbody>
</table>

Also in this analysis, it appeared that the results did not change, neither in the group as a whole nor in asthma and COPD separately. From these data, it can be concluded that regression-to-the-mean explained a negligible part of the increase in FEV₁ during steroid treatment. As the patients were selected on the combination of both a fast annual decline in FEV₁ and a high exacerbation rate, regression-to-the-mean will even be lower because the rapid fall in lung function is more likely to be a real reflection of their worsening disease.

The observed changes in FEV₁ and other parameters during BDP treatment are the consequence of a real treatment effect and not of regression-to-the-mean.

**References**

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Onmisbaar was de bemoediging, aandacht en steun van mijn ouders, niet alleen de afgelopen periode van mijn promotieonderzoek maar ook in vele jaren daarvoor. Hartelijk dank wat jullie voor mij hebben gedaan en nog steeds doen.

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Ik wil afsluiten met Degene te bedanken aan wie ik alles te danken heb. Zonder hulp van mijn hemelse Vader zou dit proefschrift nooit geschreven zijn.
Stellingen

1 Anti-inflammatoire therapie bij de lange-termijns behandeling van patiënten met astma is onontbeerlijk (dit proefschrift).

2 Introductie van eenvoudige maar betrouwbare flow-volume meters in de huisartsenpraktijk is essentieel voor de verbetering van diagnostiek en behandeling van patiënten met astma en COPD (dit proefschrift).

3 Een eenmalige bepaling van respiratoire klachten, rookgedrag, fysic-diagnostische bevindingen, kwaliteit van leven, allergie, longfunctie, reversibiliteit en bronchiale hyperreactiviteit is onvoldoende om betrouwbaar te kunnen voorspellen welke patiënten een snelle of welke een trage progressie van astma en COPD zullen vertonen (dit proefschrift).

4 Bronchiale hyperreactiviteit (gemeten aan de hand van de PC_{20}-histamine) gaat bij patiënten met astma vooraf aan (de progressie van) luchtwegobstructie terwijl bij patiënten met COPD deze functionele stoornis voornamelijk optreed als gevolg van (de progressie van) luchtwegobstructie (dit proefschrift).

5 De methode om de directe reactie op een bronchusverwijder (reversibiliteit) uit te drukken als percentage van de voorspelde FEV\textsubscript{1} discrimineert weliswaar het beste tussen patiënten met astma en COPD maar is niet onafhankelijk van de longfunctiewaarde vóór bronchusverwijding en heeft ook niet de beste reproduceerbaarheid in vergelijking met andere uitdrukkingen (dit proefschrift).

6 Bij COPD patiënten met een ongunstig ziektebeloop gedurende monotherapie met bronchusverwijders, een relatief grote reversibiliteit en meer initiële luchtwegobstructie mag een gunstig effect van behandeling met inhalatiecorticosteroïden verwacht worden (dit proefschrift).

7 Het is van belang om de ernst van astma bv. tijdens een astma-aanval niet alleen te evalueren aan de hand van 'klassieke' parameters als symptomen, longfunctie en bronchiale hyperreactiviteit maar hierin ook het dagelijks functioneren van patiënten met astma te betrekken (D. Wong-Chung, N Mateijsen, R West, L Ravell, C van Weel, Fam Pract 1992;8(4):404-408).
8 De therapietrouw en inhalatietechniek van patiënten voor inhalatiecorticoïden kunnen de beperkende factoren zijn voor het slagen van een lange-termijns behandeling met dit type middelen (dit proefschrift).

9 Het staken van een onderhoudsbehandeling met inhalatiecorticosteroïden bij patiënten met astma en COPD kan allerlei ongewenste effecten hebben: een snelle verslechtering van longfunctie, een toename in ernst en duur van exacerbaties en symptomen. Deze verschijnselen treden veelal in het eerste jaar na het stoppen op (dit proefschrift).

10 De functie van het proefschrift als kastvulling voor academici wordt zwaar onderschat.

11 De mens maakt zich eeuwig-en-altijd druk over tijdelijke dingen maar maakt zich meestal slechts tijdelijk druk over eeuwige dingen.

12 De geschiedenis van de mens in heden en verleden laat zien hoe menselijk falen de harmonie verstoort tussen de mens en zichzelf, de mens en het milieu, de mens en zijn medemens en ook de mens en God.

13 Een wereld zonder zonde zou niet zonde zijn.

14 Het dwingend principe van economische groei belemmert de werkelijke groei en bloei van hele samenlevingen en bevordert juist dat rijk en arm verder uit elkaar groeien.

15 Er zijn er die meer uitdelen dan nodig is en toch nog overhouden terwijl anderen meer inhouden dan goed is en toch tekort komen (Spreuken 11:24).

16 Een geruchtmakend Nijmeegs spreekwoord zegt: Als het regent in mei, is april gewis voorbij.

Diagnosis and treatment of patients with progressive airflow obstruction
Structure of the secretory layer above the surface epithelium of the airways. The viscous (gel) phase is arranged into a sheet (arrows) and into stringy complexes. Scanning electron micrograph (magnification 496 x).
