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## How Detrimental Is Chronic Use of Bronchodilators in Asthma and Chronic Obstructive Pulmonary Disease?

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Recently, interest in the possibly detrimental effects of chronic bronchodilator use for treating asthma and chronic obstructive pulmonary disease (COPD) has increased. It started with the observation that there was an association between the use of  $\beta$ -agonists and death from asthma (1–6). The concern increased when clinical trials reported increased bronchial hyperresponsiveness (7–9), increased decline in lung function (10), or worsened overall control of asthma during continuous use of  $\beta$ -agonists (11). Very recently, it was observed that  $\beta$ -agonists might even cause tolerance to the protective effect against provocative stimuli such as methacholine (12, 13), AMP (13), and allergen (14). All these observations have caused considerable concern among doctors and patients. News media have paid a lot of attention to the possibly detrimental effects of bronchodilators. There are many examples of patients who refuse to use their medication any more after reading frightening headlines. Therefore, it seems worth questioning how detrimental the chronic use of bronchodilators really is. How firm is the evidence for deleterious effects of these drugs? A careful review of the literature does not provide firm evidence that bronchodilators cause increased asthma morbidity or mortality.

From a meta-analysis of all available studies assessing the association between  $\beta$ -agonist use and death from asthma, Mullen and colleagues (15) concluded that there is indeed a weak but significant association between  $\beta$ -agonist use and death. The correlation between death from asthma and  $\beta$ -agonist use in 364 cases and 1,388 control subjects was  $r = 0.10$ ,  $p < 0.000001$  (15). However, this relationship only emerged when  $\beta$ -agonists were administered with a nebulizer and not with a metered-dose inhaler. As administration of  $\beta$ -agonists with a nebulizer is normally restricted to the most severe cases of asthma, it seems probable that these asthmatics were more at risk of dying from asthma than other asthmatic patients who could be treated with a metered-dose inhaler. So the severity of the disease in these patients has caused both the asthma-related death and the use of a  $\beta$ -agonist by means of a nebulizer. This problem of the direction of causality is inherent to epidemiologic studies and can only be solved by randomized clinical trials, in which indicators of the disease are studied under controlled circumstances. The significant association between death from asthma and  $\beta$ -agonist use in this meta-analysis (15) was mainly

caused by the results of Spitzer and colleagues' study (6). This study differed from the others in at least one important aspect: the subjects were older. It seems probable that older patients are more likely to rely on self-medication with bronchodilators in emergency situations or to deny the severity of an asthma emergency (15).

Some randomized clinical trials report that continuous use of bronchodilators increases bronchial hyperresponsiveness during or after using a  $\beta$ -agonist (7–9, 11). However, other studies do not support this observation (10, 16–20). If we take a closer look at the results of these studies, it seems that the more patients are involved, the less clear the adverse effect on bronchial hyperresponsiveness is. Almost all the studies that show increased bronchial hyperresponsiveness investigated fewer than 20 subjects, while studies with 53, 91, and 113 participating subjects, respectively, did not point to increased bronchial hyperresponsiveness during continuous bronchodilator use (18, 19, 10). This may imply that bronchodilators only have an adverse effect in small, selected groups of asthmatics. All the changes in hyperresponsiveness observed were between 0.5 and 1.5 doubling dose of the challenge test, which is virtually identical to the replicability of the test and therefore of doubtful clinical significance.

We conducted a randomized study that showed that continuous use of bronchodilators for 2 yr may increase the decline in lung function when compared to treatment on demand (10). No other studies comparing different forms of bronchodilator use lasted long enough to assess a yearly decline in lung function. In our study, 223 adult patients with asthma or COPD, recruited from 29 general practices, were randomly assigned to either continuous treatment (with 1600  $\mu$ g salbutamol or 160  $\mu$ g ipratropium bromide daily;  $n = 113$ ) or treatment on demand (medication only during exacerbations or periods of dyspnea;  $n = 110$ ). Patients were randomly assigned either to the group that used salbutamol during the first year and ipratropium during the second or to the group that used these drugs in reverse order (cross-over design). No differences in efficacy between the two drugs could be assessed.

A follow-up study with 56 patients, who had a high decline in lung function and a high exacerbation rate during bronchodilator use alone in the first 2 yr, clearly showed that an inhaled corticosteroid could not only slow down but also partly reverse the deterioration of asthma or COPD (21). We also followed the remaining 83 patients, who had shown to be nonsteroid-dependent in the first 2 yr, during another 2 yr of bronchodilator treatment alone (22). In these patients there was no difference at all between 4-yr continuous use of bronchodilators and use on demand with respect to decline in lung function, bronchial hyperresponsiveness, mean morning peak flow, diurnal variation of peak flow, the number of exacerbations, or experienced health (23). So the deleteri-

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ous effects of continuous use of  $\beta$ -agonists could not be demonstrated in these nonsteroid-dependent patients.

These observations clearly show that possible negative effects of bronchodilators are not as general as originally assumed (10, 11). It seems likely that some patients with asthma (and maybe also patients with COPD) are more sensitive to deleterious effects of bronchodilators than others. It is relevant to know which patients deteriorate during continuous use of a bronchodilator alone and therefore need additional medication.

In order to find out whether there are subgroups of patients who are more sensitive than others to possible deleterious effects of bronchodilators, we have analyzed our original data again (10). We performed a multivariate analysis in which the effects of several variables (such as atopy, smoking behavior, reversibility of obstruction, baseline bronchial hyperresponsiveness, baseline FEV<sub>1</sub>, peak-flow variability, age, and sex) on the decline in lung function were investigated. We assessed the separate and combined effects of these variables on the decline in lung function during use of salbutamol and of ipratropium in patients with asthma and COPD separately. We observed that only asthmatic patients who were both allergic (i.e., allergic to at least one out of seven radioallergosorbent tests to pollen from weeds, grasses, and trees; cats and dogs; house dust mites; and *Aspergillus fumigatus*) and had a high reversibility of obstruction (i.e., FEV<sub>1</sub> reversible more than 15%, 60 min after inhaling 400  $\mu$ g salbutamol and 80  $\mu$ g ipratropium bromide, compared to the baseline) had an increased decline in lung function during use of the  $\beta$ -adrenergic drug salbutamol. As this effect was independent of all other important characteristics (e.g., baseline bronchial hyperresponsiveness, baseline lung function, peak-flow variability, smoking, age, or sex), it seems probable that reversibility and allergy were not merely measures of the severity of the disease but were real determinants of an increased decline in lung function during bronchodilator use. In the Table, this is illustrated by presenting regression lines of the decline in lung function of several subgroups of patients who used salbutamol daily during 1 yr (multivariate analysis not presented). Recently, Cockcroft and colleagues observed that 2 wk of regular inhaled salbutamol increased airway responsiveness to allergen and caused tolerance to the protective effect of salbutamol on bronchoconstriction induced by allergen (14). They speculated that the enhanced airway response to allergen was due to enhanced mediator release from mast cells, possibly due to mast-cell  $\beta$ -receptor downregulation. This would mean that regular use of  $\beta$ -agonists in conjunction with exposure to allergens would induce inflammation, which in turn is an important determinant of an increased decline in lung function (24). It would also explain why  $\beta$ -agonists induce an increase in hyperresponsiveness in some patients (7–9, 11) and not in others (10, 16–20).

It seems paradoxical that especially allergic, reversible-obstruction patients should be cautious in using  $\beta$ -agonists chronically, as these patients in general will benefit most from the acute bronchodilating effect of these drugs. This allows a second explanation for the possibly deleterious effects of bronchodilators, namely a masking effect of the drug (25). If a patient is sensitive to some antigen and wheezes or gets dyspnea on exposure, his natural tendency will be to stay away from it. The bronchoconstrictive reaction to antigen will warn him against repeated exposures. If, on the other hand, the patient is given effective bronchodilator medication that allows him to "have a normal life," he will quickly learn to get rid of the wheezing when it starts or to prevent it altogether by taking the bronchodilator in advance. Because the  $\beta$ -agonist drug does not interfere with the late reaction to the inhaled substance, patients may eventually develop a progressive inflammatory airway disease with increasing bronchial hyperresponsiveness. We observed earlier that there was a correlation between the decline in lung function and the increase in bronchial symptoms in patients who had been treated on demand, but that there was no correlation at all in patients who had been treated with bronchodilators continuously (26). A poor perception of the severity of asthma seems to be a predictor of severe asthma, and it may be possible that bronchodilator drugs influence afferent signaling and its processing in the brain (27). A masking effect may be particularly important for long-acting bronchodilators, as these drugs are especially effective in treating symptoms and have occasionally been shown to suppress the subjective need for anti-inflammatory medication during chronic use (28). These (partly hypothetical) relationships are summarized in the figure.

Several international guidelines (29, 30) recommend using additional medication such as inhaled corticosteroids in case of an increased need for bronchodilators. If this recommendation is valid, it is important to know the dose of the bronchodilator inhalant at which deleterious effects will appear. In other words, at which dose is it better to use additional anti-inflammatory medication than to raise the dose of the bronchodilator? No studies have appeared on this subject thus far. In our original data (10), we therefore related the decline in lung function to the mean daily dose of salbutamol in asthmatics. Of the participating patients, 34 asthmatics used 400  $\mu$ g salbutamol between 0 and 4 times daily. We observed that only patients who used an average of more than 400  $\mu$ g salbutamol daily had an increased decline in lung function. In these patients, there was even a correlation between the mean daily dose of salbutamol and the yearly decline in lung function (average decline in FEV<sub>1</sub> of 110 ml/yr/400  $\mu$ g salbutamol). Differences in lung function decline were not caused by differences in the severity of asthma at the start of the study: there were no significant differ-

TABLE 1  
YEARLY DECLINE IN LUNG FUNCTION DURING DAILY USE OF SALBUTAMOL

Clinical Characteristics of Subgroups of Patients	Regression Line	p Value	Correlation Coefficient	n
Reversibility $\geq 15\%$ * + atopy	$y = -150x + 408$	0.02	0.36	14
Ex/nonsmoker + reversibility $\geq 15\%$ *	$y = -108x + 303$	0.08	0.18	18
Ex/nonsmoker + atopy	$y = -101x + 220$	0.14	0.15	16
Reversibility $\geq 15\%$ * + hyperresponsiveness <sup>†</sup>	$y = -62x + 73$	0.37	0.07	13
Ex/nonsmoker + hyperresponsiveness <sup>†</sup>	$y = -61x + 73$	0.37	0.07	18
Atopy + hyperresponsiveness <sup>†</sup>	$y = -7x - 18$	0.93	0.03	13

Table summarizes yearly decline of several subgroups of asthmatic patients. The change in FEV<sub>1</sub> in ml/yr (y), the mean daily dose of salbutamol given in increments of 400  $\mu$ g (x), and the corresponding correlation coefficients are given.

\* Reversibility of FEV<sub>1</sub> 60 min after inhaling 400  $\mu$ g salbutamol and 80  $\mu$ g ipratropium bromide compared to the baseline.

<sup>†</sup> Bronchially hyperresponsive: PC<sub>20</sub>  $\leq 2$  mg/ml.

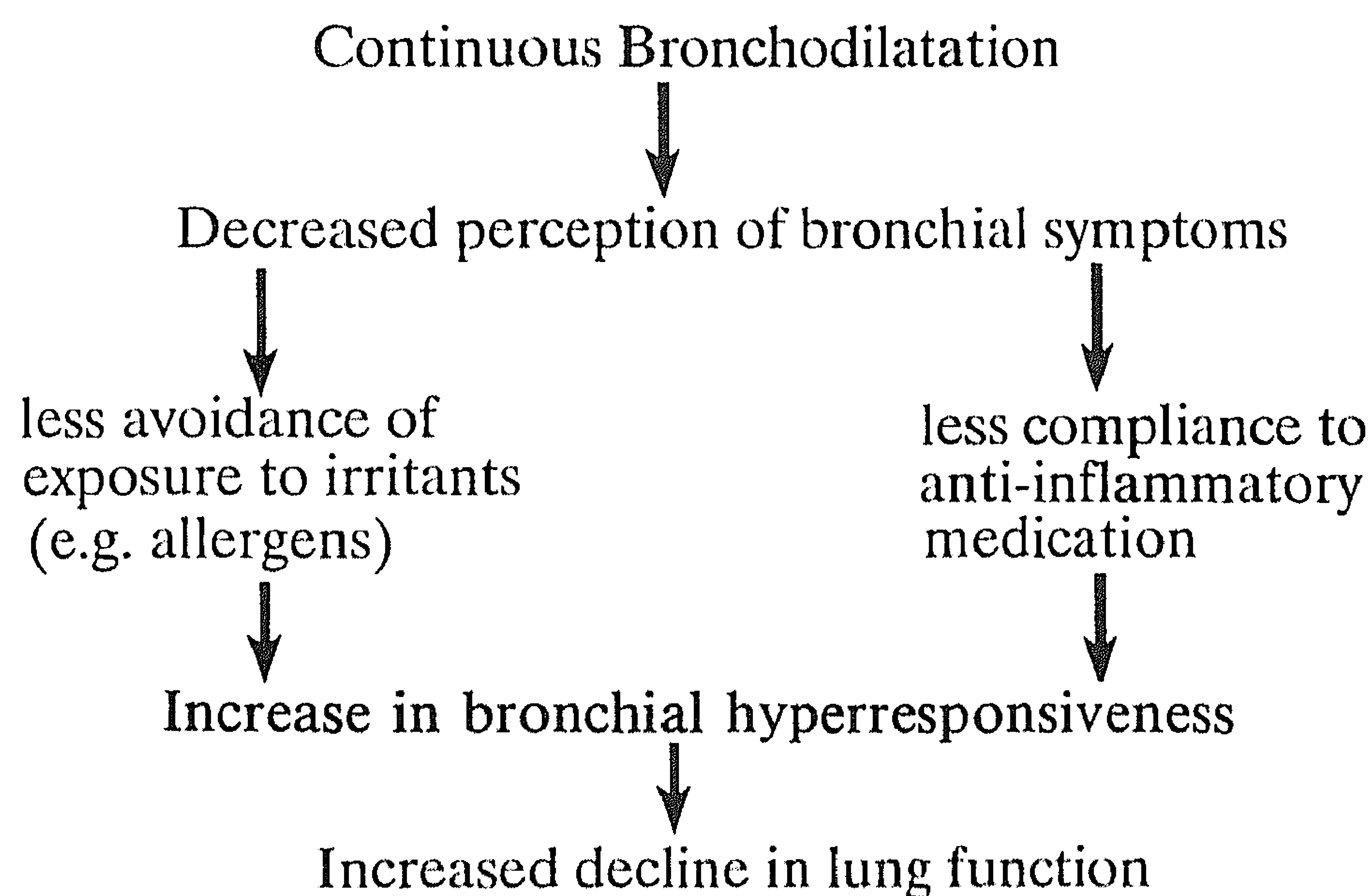


Figure.

ences in lung function, bronchial hyperresponsiveness, or symptoms between patients who rarely needed medication and patients who needed medication more than once daily. These findings clearly confirm the advice proposed by the British Thoracic Society (29) to use additional anti-inflammatory medication if patients need a bronchodilator more than once daily (e.g., salbutamol 400 µg daily). This observation also points to the paradox already mentioned: patients who need bronchodilator medications most seem to be most sensitive to their deleterious effects.

There are indications that the incidence of asthma is still rising (31), and it is clear that the use of bronchodilators has tremendously increased in the past decade (32). However, the available data do not provide firm evidence that the use of bronchodilators itself causes this increased morbidity. It seems more logical that the increased morbidity demands intensified therapy. There may be one exception: there are indications that chronic use of  $\beta_2$ -agonists increases the severity of asthma in allergic patients with reversible obstruction. This could be explained by several underlying pathophysiologic mechanisms, which should be investigated. Patients should be carefully instructed to inform their physician when they need a bronchodilator more than once daily. When there is not undue reliance on bronchodilators, the general concern among patients and doctors about chronic use of these drugs does not seem to be justified.

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