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Comparative Effects of a Two-Week Treatment with Nebivolol and Nifedipine in Hypertensive Patients Suffering from COPD

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Key Words
Arterial hypertension · Chronic obstructive pulmonary disease · Nebivolol · Nifedipine · Salbutamol

Abstract
Background: It has been suggested that the antihypertensive agent nebivolol, a β_1-adrenoceptor-blocking agent that modulates the endogenous production of nitric oxide, is preferable to 'conventional' β_1-blockers in hypertensive patients with airway dysfunction. ***Objectives:*** Since β_1-blockade by nebivolol is larger after repeated dosing than after a single oral intake, we have explored its effect on pulmonary function after a 2-week treatment in hypertensive patients with mild to moderate COPD. ***Methods:*** A single-blind crossover design was used. Twenty patients with COPD as selected above and with a diastolic blood pressure of 95–110 mm Hg after 1 week of placebo run-in were entered into the two 2-week active treatment periods with either 5 mg nebivolol (n = 10) or 30 mg nifedipine gastrointestinal-transport-system (GITS) (n = 10) taken for a period of 2 weeks. After a further 1-week washout, subjects were crossed-over to receive the other drug for 2 additional weeks. At each visit, changes in spirometric indexes and the interaction with the bronchodilator effect of salbutamol were investigated. Moreover, systolic and diastolic blood pressure (BP) together with heart rate were manually measured in order to evaluate the cardiovascular effects of the different treatments. Throughout the study, patients recorded symptoms. ***Results:*** Similar and significant reductions in systolic and diastolic BP were observed with both treatments. The impact of nifedipine on FEV_1 was not significant ($p > 0.05$), while that of nebivolol was slight. The maximum response to salbutamol was slightly decreased with either nebivolol or nifedipine GITS. Day-to-day airway obstruction control, interpreted from patient recordings of symptom scores and inhaler use, was similar with both treatments. ***Conclusions:*** Our pilot study suggests that the use of nebivolol in hypertensive patients with stable mild to moderate COPD was safe during a 2-week trial. Evaluation of longer time periods, larger patient numbers with more severe COPD or during exacerbations is warranted.

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Introduction

The concomitant prevalence of arterial hypertension and chronic obstructive pulmonary disease (COPD) is far from unusual. Antonelli Incalzi et al. [1] reported that 28% of 270 patients consecutively discharged from a University Hospital after an acute exacerbation of COPD were suffering from hypertension. Meier et al. [2] determined the prevalence of comorbid conditions and antihypertensive prescribing patterns for 7,526 patients receiving antihypertensive medication at four Department of Veterans Affairs clinics in USA. Among these hypertensives, 1,553 had COPD or asthma.

Despite clear evidence of the effectiveness of β-adrenoceptor blockers in the management of arterial hypertension, clinicians often hesitate to administer them in the presence of COPD because lung function can even be reduced by a selective β_1-adrenoceptor blocker [3]. However, if the benefits of these agents are felt to be substantial for a patient with bronchospastic disease, the lowest dose of a selective β_1-adrenoceptor blocking drug with no positive intrinsic sympathomimetic activity (i.e., metoprolol, atenolol, esmolol) and the concomitant use of high doses of a β_2-agonist may outweigh risks in some patients with well-controlled COPD [4]. In effect, a selective β_1-adrenoceptor-blocking drug usually has over 20 times more affinity for β_1-receptors than for β_2-receptors, and theoretically should entail significantly less risk for bronchoconstriction [5]. β_1-Adrenoceptor blocking agents with ancillary properties, such as β_2-agonist activity and/or the modulation of endogenous production of nitric oxide (NO), could be preferable to 'conventional' β_1-blockers. However, they may elicit bronchospasm in some individuals and impair the bronchodilator response to inhaled β_2-agonists [6].

Nebivolol, a new selective β_1-adrenoceptor blocking agent that does not show intrinsic sympathomimetic activity, is endowed with the modulation of the endogenous production of NO. In particular, it has been demonstrated that nebivolol vasodilates human forearm vasculature via the *L*-arginine/NO pathway [7]. Nebivolol does not significantly decrease airway conductance compared with atenolol and propranolol [7]. In 6 healthy volunteers, unlike propranolol and atenolol, it did not antagonize salbutamol effects [8]. Recently, we have investigated the respiratory tolerance of nebivolol in 12 asthmatic patients [9]. It slightly affected airway function. However, although its effect on FEV_1 was statistically significant, the mean percent decrease (–8.4%) was small. Nevertheless, nebivolol partially antagonized the bronchodilator response to inhaled salbutamol, but this effect was similar to that elicited by celiprolol.

Since β_1-blockade by nebivolol is larger after repeated dosing than after a single oral intake [10], we have explored the effects of a 2-week treatment with nebivolol (5 mg) once daily in hypertensive outpatients also suffering from COPD.

Patients and Methods

Twenty patients, 13 males and 7 females aged 47–75 years, were recruited among subjects who regularly visited outpatient lung disease clinics at our hospitals over several months. They met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of moderate COPD [11] and were also suffering from arterial hypertension. Exclusion criteria were: current evidence of asthma as primary diagnosis, unstable respiratory disease requiring oral/parenteral corticosteroids within the 4 weeks prior to commencing the study, upper or lower respiratory tract infection within the 4 weeks of the screening visit, concurrent use of medications that affect COPD, evidence of alcohol abuse.

The study was conducted in accordance with guidelines for good clinical practice issued by the European Commission, in 1990, and with the Declaration of Helsinki of 1975, as revised in 1983. Approval from the ethics committee was obtained, and all patients gave written informed consent for their participation.

Thereafter, the candidates stopped previous antihypertensive medications (ACE inhibitors or diuretics) and received placebo for 1 week. Only those with an average of three sitting diastolic blood pressure (BP) measurements of 95–110 mm Hg after 1 week of placebo run-in were entered into the two 2-week active treatment periods. Patients were randomly allocated to take either 5 mg nebivolol (n = 10) or 30 mg nifedipine, administered in a long-acting gastrointestinal-transport-system (GITS) formulation (n = 10) taken once daily at 8 a.m. as the first active drug for a period of 2 weeks, i.e., a time interval sufficient to reach a steady state. After a further 1-week washout, subjects were crossed over, based on prior randomization, to receive the other drug for 2 additional weeks. The dosages of nebivolol and nifedipine used in this trial are those that are usually prescribed for the treatment of arterial hypertension.

Patients were seen on 7 occasions: at enrolment; after the 1-week run-in period, when they were randomized into the active treatment groups if the entry criteria had been fulfilled; after 1 and 2 weeks of the first treatment; after 1 week of washout, and after 1 and 2 weeks of the second treatment. Visits were always performed between 1 and 2 p.m., that is 5 h after the intake of drug.

At each visit, patients performed standard spirometry, followed by spirometry after incremental doses of salbutamol of 200, 200, and 400 μg (i.e., total cumulative doses of 200, 400, and 800 μg) in order to construct a dose-response curve. Salbutamol was administered from a metered-dose inhaler and holding chamber (AeroChamber; Trudell Medical International, London, Ont., Canada) with a mouthpiece. Dose increments were given at 20-min intervals with measurements being made 15 min after the administration of each dose. Three acceptable forced expiratory maneuvres were performed in order to obtain two reproducible results for forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), and forced expiratory

flow rate at 50% of FVC. The highest FEV_1, obtained from one or the other of the reproducible curves, was kept for analysis. Systolic and diastolic BP together with heart rate were manually measured in order to evaluate the cardiovascular effects of the different treatments.

Throughout the study, patients used a diary card. They daily recorded the following 6 symptoms: the ability to perform the usual daily activities; breathlessness over the previous 24 h; waking at night due to respiratory symptoms; breathlessness on rising; cough, and sputum production. The scoring system for each symptom allowed values in the range from 0 (no symptoms) to 3 (worst), and the 6 questions allowed for up to a maximum total score of 18 per day.

Four patients receiving chronic inhaled corticosteroid treatment were instructed to remain on that treatment throughout the study. Inhaled salbutamol (100 μg per puff) was the only allowed bronchodilator. Patients recorded the consumption of salbutamol (number of inhalations) in their diary cards. Salbutamol was withheld for at least 6 h prior to each visit.

The maximum FEV_1 at each visit was chosen as the primary outcome variable to compare the two treatments. Analyses of spirometric data and those of heart rate, systolic BP, and diastolic BP for each treatment were performed using Student's t test for paired variables. Mean responses were also compared by multifactorial analysis of variance to establish any significant overall effect among treatments. In the presence of a significant overall analysis of variance, Duncan's multiple range testing with 95% confidence limits was used to identify significant differences. A probability level of $p < 0.05$ was considered to be significant for all tests. All data analyses were performed using computer software (GB-STAT, version 8.0; Dynamic Microsystems, Silver Spring, Md., USA). The number of enrolled patients for this study was not calculated because it was a pilot investigation.

Results

All patients completed the study. They remained in clinically stable condition throughout the study and did not notice any side effects. No patient became symptomatic from shortness of breath. There were no significant differences between the baseline spirometric values of the two treatment groups ($p > 0.05$).

Nebivolol and nifedipine elicited a decrease in FEV_1 after a 2-week treatment (fig. 1) (mean difference for nebivolol, –0.109 liter [95% confidence interval (CI) –0.043 to –0.175]; mean difference for nifedipine, –0.028 liter [95% CI 0.016 to –0.072]). The effect of nifedipine on FEV_1 was considered not to be significant ($p > 0.05$), but nebivolol was considered to be significant ($p < 0.05$). However, the mean decrease in FEV_1 after nebivolol administration (–9.4%) was slight, and, likely, it does not have a true clinical significance on patients with COPD. There was a statistically significant difference ($p < 0.05$) after the 2-week treatment between the results observed with nebivolol and nifedipine. Nebivolol also induced a slight mean decrease in FVC (–0.084 liter [95% CI –0.019 to –0.149]) that was significant ($p < 0.05$), whereas the mean change in FVC after nifedipine (–0.029 liter [95% CI 0.034 to –0.092]) was not significant ($p > 0.05$).

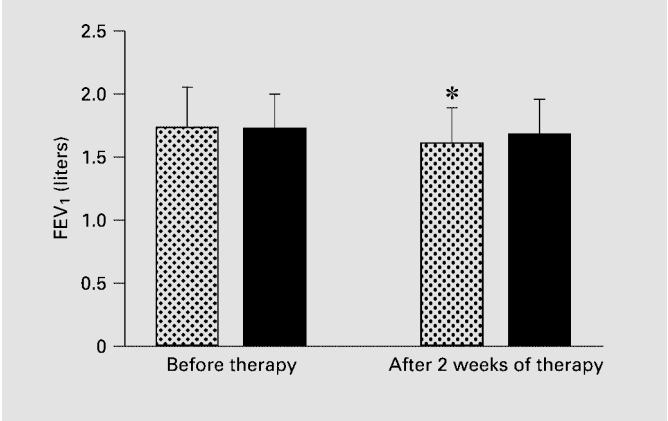

Fig. 1. FEV_1 before and after a 2-week therapy with nebivolol 5 mg (▨), or nifedipine GITS 30 mg (■) once daily. * $p < 0.05$ vs. baseline.

At the end of the 2-week treatment with nebivolol or nifedipine, the dose-response curves to inhaled salbutamol for FEV_1 showed a statistically significant shift to the right when compared to those obtained before each treatment, and the maximum response to salbutamol was decreased (fig. 2). The mean difference between the highest salbutamol FEV_1 value before and after treatment with nebivolol (–0.178 liter [95% CI –0.100 to –0.256]) was statistically significant ($p < 0.05$). Also, the mean difference between the highest FEV_1 value elicited by salbutamol inhalation before and after 2-week nifedipine treatment (–0.048 liter [95% CI –0.011 to –0.084]) was statistically significant ($p < 0.05$).

The mean numbers of puffs of salbutamol inhaled per day were 3.7 (95% CI 2.2–5.2) before and 4.8 (95% CI 3.3–6.3) after nebivolol, and 4.1 (95% CI 2.4–5.8) before and 4.5 (95% CI 3.0–6.0) after nifedipine (table 1). Use of salbutamol was not significantly different when comparing the two treatments.

The mean symptom scores were 6.75 (95% CI 5.93–7.57) and 6.85 (95% CI 6.22–7.48) before receiving nebivolol or nifepidine, respectively, and 7.20 (95% CI 6.58–7.82) and 6.90 (95% CI 6.24–7.56) at the end of the nebivolol and nifepidine treatments, respectively (table 1). There was no statistically significant difference among the treatment groups.

Each treatment reduced the BP significantly and to a comparable degree (table 2).

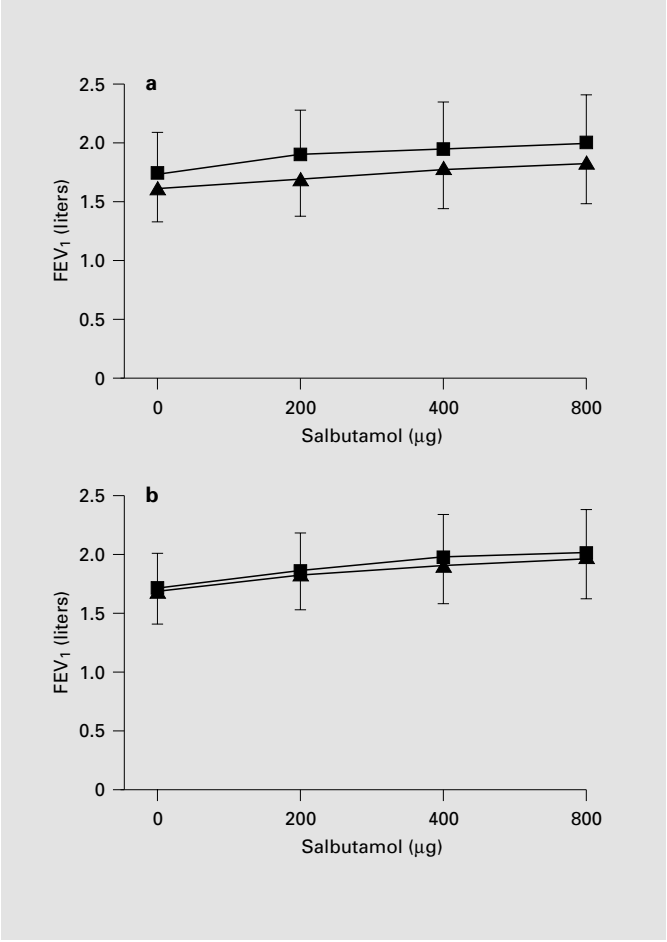

Fig. 2. Mean (± SD) dose-response curves to inhaled salbutamol for FEV_1 constructed before (■) the 2-week treatment period and 5 h after (▲) the last administration of nebivolol 5 mg (**a**), or nifedipine GITS 30 mg (**b**) once daily.

Discussion

When a β-adrenoceptor blocker is really necessary in hypertensive patients with COPD (for instance, in the presence of myocardial infarction, congestive heart failure, cardiac arrhythmia, and thyrotoxicosis), a β_1-adrenoceptor-selective blocker is preferred in combination with bronchodilator agents [6, 12]. In fact, the available evidence suggests that cardioselective β-blockers given to patients with COPD do not produce a significant short-term reduction in airway function or in the occurrence of COPD exacerbations [13]. This is not a surprise because most of the adverse pulmonary effects exerted by β-adrenoceptor-blocking drugs in patients with airway dysfunction are related to interference with β_2-adrenoceptor-mediated bronchodilation [6]. Nevertheless, it has been established that no β-blocker is entirely safe in patients with COPD [14–18], although the cumulative evidence from two meta-analyses indicates that cardioselective β-blockers should not be withheld in patients with reactive airway disease or COPD [13, 19].

In any case, the American College of Chest Physicians recommendations affirm that the application of α,β-blockers with α-blocking activity, such as atenolol, labetalol, nebivolol, and doxazosin, in hypertensive patients with compromised pulmonary function is warranted [3]. It must be highlighted that, although the American College of Chest Physicians considers nebivolol as an α,β-blocker with α-blocking activity [3], α-adrenergic receptors are not involved in the vasodilating effect of nebivolol [10, 20]. Moreover, the role of α-adrenoceptors in regulating human airway function is questionable [21].

Table 1. Number of puffs of salbutamol inhaled per day and symptom scores before and after a 2-week therapy with nebivolol or nifedipine in 20 hypertensive patients suffering from mild to moderate COPD (means and 95% CI in parentheses)

	Nebivolol	Nifedipine
Puffs of salbutamol		
Before therapy	3.7 (2.2–5.2)	4.1 (2.4–5.8)
After 2-week therapy	4.8 (3.3–6.3)	4.5 (3.0–6.0)
Symptom scores		
Before therapy	6.75 (5.93–7.57)	6.85 (6.22–7.48)
After 2-week therapy	7.20 (6.58–7.82)	6.90 (6.24–7.56)

Table 2. Blood pressure before and after 2-week therapy with nebivolol or nifedipine in 20 hypertensive patients suffering from mild to moderately severe COPD (means and 95% CI in parentheses)

	Nebivolol	Nifedipine
PAS, mm Hg		
Before therapy	158.5 (155.1–161.9)	159.3 (156.5–162.0)
After 2-week therapy	147.0 (143.7–150.3)	147.5 (144.1–150.9)
PAD, mm Hg		
Before therapy	101.5 (99.1–103.9)	100.8 (98.3–103.2)
After 2-week therapy	87.2 (83.8–90.7)	89.5 (86.8–92.2)

This study has shown that the impact of nebivolol on respiratory function in patients with COPD is slight, as assessed by FEV_1 changes, incidence of symptoms and use of inhaled salbutamol. Although there was a significant difference between treatments in the mean FEV_1, the recorded use of salbutamol and the mean score of symptoms show that the control of disease after nebivolol was not different from that after nifedipine. This is an important finding because nifedipine is suggested as first choice in COPD patients [6] considering that it may elicit mild bronchodilation in these subjects [22].

Several potential pharmacologic actions could justify why nebivolol could be considered in COPD patients, but also the type of bronchial obstruction is important. In fact, the bronchoconstrictor response to a given β-adrenoceptor-blocking agent occurs mainly in patients with reversible bronchial obstruction and it is much less pronounced in those with irreversible, or partially reversible bronchial obstruction. Translated into terms of clinical diagnosis, this means that problems should be expected in patients with bronchial asthma, whereas those with COPD are much less likely to develop relevant symptoms [23].

The potent effects of NO on vascular smooth muscle and its presence in the major conducting airways raise the possibility that it could contribute to regulation of airway smooth muscle tone [24]. However, Dal Negro et al. [25] have shown that a single nebivolol dose does not appear to affect the production of exhaled NO in patients with mild to moderate asthma. In any case, the increase of NO levels in COPD patients does not seem to be useful [26].

Other actions could explain why the impact of nebivolol on airways is mild. It has been documented that metabolized nebivolol induces a β_2-adrenergic-receptor-mediated rise in endothelial cytosolic free Ca^{2+} concentration and, consequently, it augments NO production [27]. Therefore, we speculate whether nebivolol also interacts with β_2-adrenergic receptors on airways. On the other hand, nebivolol is a potent stimulator of endothelial nitric oxide synthase (NOS) and exerts this effect via 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptors [28]. The question is whether nebivolol might interact with 5-HT_{1A} receptors on the airways. In this case, we could speculate that nebivolol activates prejunctional β_2-adrenoceptors leading to inhibition of cholinergic neurotransmission [29], and postjunctional β_2-adrenoceptors inducing direct bronchodilation. Besides, it might stimulate 5-HT_{1A} receptors on airway smooth muscle and it is well known that direct relaxant effects of 5-HT in human tracheal and bronchial tissue are probably due to the activation of 5-HT_{1A} receptors [30].

In conclusion, our pilot study on 20 patients with COPD indicates that it is possible to suggest the use of nebivolol in hypertensive patients with COPD when a β-adrenoceptor blocker is a necessity. However, in our selected COPD patient population nebivolol produced a small decrease in FEV_1 (–9.4%) compared with the preexisting airflow limitation, suggesting caution should be applied in interpreting our results. We examined the effects of nebivolol on the airways for only 2 weeks because we were hesitant about imposing a lengthy β-adrenoceptor blocker treatment on patients who had COPD. Therefore, we do not know if these effects could become more apparent over a longer time interval. In effect, the study was too short for testing for an effect on the frequency and severity of acute exacerbations of COPD. We must also stress that all our patients had substantial levels of airway obstruction, but we excluded subjects with more severe COPD (severe or very severe stage according to the GOLD classification [11]). Our choice was dictated by the necessity to explore the effects of nebivolol in a less dangerous clinical condition because the present trial, as we have already highlighted, was a pilot study. As a consequence, we cannot exclude that patients with more severe COPD may suffer substantially greater alteration of airway function with nebivolol treatment.

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