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RESEARCH ARTICLE

# The use of reversibility percent in spirometric assessment of chronic obstructive pulmonary diseases for the detrimental effect of 3rd generation beta-blockers

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## ABSTRACT

**Background:** For clinicians who work in respiratory medicine, the use of beta-blockers (BBs) has, for a long time, posed a dilemma because of the potential risk of bronchospasm and neutralization of the effectiveness of β-2 agonists. **Aims and Objectives:** To observe the effect of nebivolol on clinical and spirometric parameters on patients with stable chronic obstructive pulmonary disease (COPD) and the effect of the reversibility magnitude on the nebivolol detrimental effects. **Materials and Methods:** A total of 32 patients with age above 40 years regardless their smoking state from both genders were included in the study at College of Medicine, Babylon University from February 2014 to September 2016. The study was approved by Institutional Review Board. The study included the patients who were diagnosed as COPD. Patients were divided into two groups depending on the reversibility test in spirometric assessment. **Results:** There were significant differences between means of forced expiratory flow (FEF), forced expiratory volume in 1 second (FEV1) and COPD assessment test (CAT) score before and after using of 3rd generation BB for all patients with COPD and patients with high reversibility percent while for patients with low reversibility percent were significant differences between means of FEF, while there were no significant differences between means of FEV1 and CAT score. **Conclusion:** The reversibility percent can be used as an indicator for the adverse effect of BB on COPD patients.

**KEY WORDS:** Reversibility Test; Chronic Obstructive Pulmonary Disease; Nebivolol; Outcome Predictor

## INTRODUCTION

For clinicians who work in respiratory medicine, the use of beta-receptor blockers (BBs) has, for a long time, posed a dilemma because of the potential risk of bronchospasm and neutralization of the effectiveness of β-2 agonists.[1] This matter is different and a particularly challenging in patients with chronic obstructive pulmonary disease (COPD) whom many of them have substantial cardiovascular comorbidity,[1] and in whom the avoidance of BB might deprive them of substantial cardiovascular benefit.[2] While caution is generally the reasonable practice in drug safety, this is not so here, as one would be withholding a treatment that has a proved effect for cardiovascular disease.[3,4]

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BBs have been shown to reduce mortality in patients with hypertension, heart failure, and coronary artery disease.[5,6] They are also useful in the management of arrhythmias, thyrotoxicosis, and to reduce complications in the perioperative period.[7-9] Despite the overwhelming evidence for these benefits, BBs are used in clinical practice, as of all patients discharged after surviving a myocardial infarction (MI), only 40% were prescribed BB.[10]

The most common comorbid conditions associated with withholding BBs in elderly patients after MI are COPD and asthma, while peripheral arterial and bronchial problems are reported to be the leading side effects.[10] On the other hand, many patients are diagnosed and treated for COPD with no objective evidence, such as pulmonary function tests (PFT) or specialist assessment, to confirm the diagnosis, as recommended by most thoracic societies. This may indicate that a significant number of the patients are deprived the prognostic benefits of using BBs.[10]

However, recent studies indicate that BB use in patients with COPD can decrease outpatient visits and either decrease or have no effect on the number of hospitalizations. Long-term treatment with BB has been shown to increase survival and decrease exacerbations in patients with COPD.[10]

Despite the clear evidence of BBs effectiveness, there is a general reluctance to use them in patients with COPD due to a perceived contraindication and fear of inducing adverse reactions and bronchospasm. BBs are well tolerated in patients with cardiac disease and concomitant COPD with no evidence of worsening of respiratory symptoms or forced expiratory volume in 1 second (FEV1), and the safety of BBs in patients with COPD has been demonstrated, but their use in this group of patients remains low. The cumulative evidence from trials and meta-analysis indicates that cardioselective BBs should not be withheld in patients with reactive airway disease or COPD.[9]

The 1st generation agents (such as propranolol, sotalol, timolol, and nadolol), are nonselective and block β1- and β2-receptors. Blocking β1-receptors affects the heart rate, conduction, and contractility, while blocking β2-receptors, tends to cause smooth muscle contraction, therefore, bronchospasm in predisposed individuals.[5]

The 2nd generation agents or the cardioselective agents (such as atenolol, bisoprolol, celiprolol, and metoprolol) block β1-receptors in low doses but are capable of blocking β2-receptors in higher doses. This selective mode of action makes the use of these agents more suitable in patients with chronic lung disease or those with insulin-requiring diabetes mellitus. Cardioselectivity varies between agents with the bisoprolol among the most selective.[5]

The 3rd generation agents have vasodilatory properties there action is either selective (nebivolol) or nonselective (carvedilol and labetalol). The vasodilatory properties are mediated either by nitric oxide release as for nebivolol or carvedilol[5,10] or by added alpha-adrenergic blockade as in labetalol and carvedilol. A third vasodilatory mechanism, as in pindolol and acebutolol, acts via β2-intrinsic sympathomimetic activity. These BBs, therefore, have the capacity to stimulate as well as to block adrenergic receptors and tend to cause less bradycardia than the other BBs and may cause less coldness of the extremities.[7]

**Predictors of BBs Adverse Effects in COPD Patients**

A meta-analysis performed by Salpeter et al. in 2002 where randomized, blinded, placebo-controlled trials that studied the effects of cardioselective BBs on FEV1, symptoms, and the use of inhaled β2-agonists in patients with reactive airway disease were selected. The study concluded that cardioselective BBs do not produce clinically significant adverse respiratory effects in patients with mild to moderate reactive airway disease and that they should not be withheld from these patients. The studies were not designed to make recommendations about people with significant chronic airway obstruction.[11]

In another meta-analysis performed by Salpeter et al. in 2003 concluded that cardioselective BBs produced no significant change in FEV1 or respiratory symptoms compared to placebo and did not significantly affect the FEV1 treatment response to β2-agonists. Subgroup analysis revealed no significant change in results for those participants with severe COPD or for those with a reversible obstructive component. The conclusion was again that cardioselective BBs given to COPD patients do not produce a significant reduction in airway function or an increase in the incidence of COPD exacerbations. However, the selectivity of cardioselective BBs can be compromised when given in high doses or due to drug-drug interactions.[12]

The reversibility magnitude in PFT as an indicator for the airway reactivity: Is not studied well as most practice try to avoid any BB in airway disease with positive reversibility test.[10]

Hence, this study was planned with the aim of observing the effect of nebivolol on clinical and spirometric parameters on patients with stable COPD with some degree of reversibility and the effect of the reversibility magnitude on the nebivolol adverse effects.

## MATERIALS AND METHODS

A total of 32 patients with age above 40 years regardless their smoking state from both genders were included in the study at College of Medicine, Babylon University from February 2014 to September 2016. The study was approved by Institutional Review Board. The study included the patients who were diagnosed as COPD by the diagnosis of COPD is confirmed by the following:[1] (a) Spirometry demonstrating airflow limitation (i.e., a FEV1/forced vital capacity [FVC] ratio <0.7 plus an FEV1 <80% of predicted) that is incompletely reversible (<12%) after the administration of an inhaled bronchodilator; and (b) absence of an alternative explanation for the symptoms and airflow limitation.

Patients with stable COPD patients with Grade A or B were included in the study. They were defined as below:[1]

Group A: Low risk, less symptoms: Typically global initiative for chronic obstructive lung disease (GOLD) 1 or GOLD 2 (mild or moderate airflow limitation, i.e., post-bronchodilator FEV1 >50%) and 0-1 exacerbation/year and no hospitalization for exacerbation; and COPD assessment test (CAT) score <10.

Group B: Low risk, more symptoms: Typically GOLD 1 or GOLD 2 (mild or moderate airflow limitation, i.e., post-bronchodilator FEV1 >50%) and 0-1 exacerbation/year and no hospitalization for exacerbation; and CAT score ≥10.

Both types of patients were on regular use of tiotropium inhaler twice daily plus on need short-acting beta agonists (SABA). Need of nebivolol treatment 5 mg/day for hypertension in 19 patients (hypertension diagnosed by 2 reading of blood pressure in standard condition 24 h apart) or for ischemic heart disease for the other 13 patients (diagnosed by conventional coronary angiography with a significant one or more vessels obstructive lesions).

The assessment was done at zero points (when the patients selected according to the above criteria and need to start nebivolol treatment) by,

- Age, gender, and smoking state
- CAT score using the attached Arabic questionnaire version
- Spirometric using SpiroLab III in setting position with closed nose and the test repeated 15 min after nebulization with 5 mg salbutamol solution, and 3 parameters were selected FVC, FEV1 to measure the ratio FEV1/FVC and forced expiratory flow (FEF) 50 as a reflection to small airway disease and all patient with reversibility <12% were selected for more evaluation.

The patients were divided into two groups: (i) Group 1 with a high percent of reversibility between 6% and 12%; and (ii) Group 2 with low percent of reversibility between 1% and 5%. The class was pointed depending on new GOLD system. Then, the same assessment was repeated after 6 months of nebivolol 5 mg treatment plus asking about: (a) Respiratory related hospitalization; (b) exacerbation: Either due to increase in sputum volume, purulence or increasing cough or shortness of breath that need additional treatment; and (c) change in the on need SABA treatment as increase in frequency of use or a sense of reduced SABA efficacy.

Data were expressed as absolute numbers with or without percentages, as means with standard deviation. Frequency comparisons were performed by an appropriate test such as Chi-square test and *t*-test. A $P < 0.05$ was considered to denote statistical significance.

## RESULTS

As shown in Table 1 the distribution of patients with COPD according to age, gender and smoking show mean age was (69.43 ± 6.1), and majority of patients (59.4%) were males and smokers as the major risk factor for CODP is smoking which is more in male and exert its effect in the older age with significant time of exposure.

The distribution of all patients with COPD according to clinical exacerbation after treatment, hospitalization after treatment and change in response to bronchodilator after treatment, as shown in Table 2, the overall exacerbation is seen in 28% of all patients, but only 1 patient need hospitalization. The change in the response to bronchodilator is seen in 18% only.

As shown in Table 3 the distribution of patients with COPD according to reversibility. More than a half of patients (56.3%) presented with the percent of 6-12 which is regarded as low reversibility while the other 43.7% have more than 6% which is labeled as high reversibility percent. Mean differences of age (years) by reversibility score including score (6-12 and <6). There were no significant differences between means of age by study groups, i.e., the two groups are matched.

**Table 1:** The distribution of patients with COPD according to sociodemographic characteristics

| Sociodemographic characteristics | *n* (%) |
|---|---|
| Age (years) | 56-81 |
| Mean±SD | 69.43±6.1 |
| Gender | |
| Male | 19 (59.4) |
| Female | 13 (40.6) |
| Total | 32 (100.0) |
| Smoking habit | |
| Smoker | 19 (59.4) |
| X-smoker | 13 (40.6) |
| Total | 32 (100.0) |

COPD: Chronic obstructive pulmonary disease, SD: Standard deviation

**Table 2:** Distribution of all patients according to study variables

| Study variables | *n* (%) |
|---|---|
| Clinical exacerbation after using of beta-blocker | |
| Yes | 9 (28.1) |
| No | 23 (71.9) |
| Total | 32 (100.0) |
| Hospitalization after using of beta-blocker | |
| Yes | 1 (3.1) |
| No | 31 (96.9) |
| Total | 32 (100.0) |
| Response to bronchodilator with beta-blocker use | |
| Yes | 6 (18.8) |
| No | 26 (81.2) |
| Total | 32 (100.0) |

Table 4 shows the association between the two studies groups and study variables including (gender, exacerbation, hospitalization, and bronchodilator response). There was no significant association between study groups and study variables.

Figure 1 shows the distribution of all patients with COPD according to class before and after treatment. About (28.1%) of patients change to Class D after using of 3rd generation BB.

There were significant differences between means of FEF, FEV1, and CAT score before and after using of 3rd generation BB as shown in Table 5 as expected there is deterioration in with the use of a respiratory depressor drug in patients with respiratory disease.

Table 6 shows mean differences of FEF, FEV1, and CAT score before and after using of 3rd generation BB for Group 1 which are significant differences between means of FEF, FEV1 and CAT score before and after using of 3rd generation BB for patients with a high percent of reversibility.

Table 7 shows mean differences of FEF, FEV1, and CAT score before and after using of 3rd generation BB for Group 2 that were significant differences between means of FEF, while there were no significant differences between means of FEV1 and CAT score before and after using of 3rd generation BB for patients with low percent of reversibility mean the patients with low reversibility percent show only significant change on the base of small airway disease but not on the major indicator, i.e., FEV1 and not on the symptomatic score measured by the CAT score.

About (38.8%) of patients change to Class D after using of 3rd generation BB in Group 1 while only (14.3%) of patients change to Class D after using of 3rd generation BB in Group 2.

**Table 3:** The mean differences of age by study groups

| Variable | Study groups | *n* | Mean±SD | *t*-test | *P* value |
|---|---|---|---|---|---|
| Age (years) | 6-12 | 18 | 71.05±6.31 | 1.756 | 0.089 |
| | <6 | 14 | 67.35±5.34 | | |

SD: Standard deviation

**Table 4:** Association between study groups and study variables

| Study variables | Study groups | | $\chi^2$ | *P* value |
|---|---|---|---|---|
| | 6-12 | <6 | | |
| Gender | | | 0.249 | 0.618 |
| Male | 10 (55.6) | 9 (64.3) | | |
| Female | 8 (44.4) | 5 (35.7) | | |
| Smoking habit | | | 0.249 | 0.618 |
| Smoker | 10 (55.6) | 9 (64.3) | | |
| X-smoker | 8 (44.4) | 5 (35.7) | | |
| Exacerbation | | | | 0.235[f] |
| Present | 7 (38.9) | 2 (14.3) | | |
| Absent | 11 (61.1) | 12 (85.7) | | |
| Hospitalization | | | | 1.000[f] |
| Present | 1 (5.6) | 0 (0.0) | | |
| Absent | 17 (94.4) | 14 (100.0) | | |
| Bronchodilator response | | | | 0.196 |
| Present | 5 (27.8) | 1 (7.1) | | |
| Absent | 13 (72.2) | 13 (92.9) | | |

Fisher's exact test

## DISCUSSION

In this study, show mean age was (69.43 ± 6.1), and the majority of patients (59.4%) were males and smokers.

**Table 5:** The mean differences of FEF, FEV1, and CAT score before and after using of beta-blocker

| Variable | Categories | *n* | Mean±SD | Paired *t*-test | *P* value |
|---|---|---|---|---|---|
| FEF | Before treatment | 32 | 59.13±13.69 | 5.355 | <0.001* |
| | After treatment | 32 | 55.31±11.78 | | |
| FEV1 | Before treatment | 32 | 69.46±11.93 | 4.388 | <0.001* |
| | After treatment | 32 | 63.40±17.36 | | |
| CAT-score | Before treatment | 32 | 16.75±7.22 | −5.149 | <0.001* |
| | After treatment | 32 | 21.53±5.50 | | |

FEF: Forced expiratory flow, FEV1: Forced expiratory volume in 1 second, CAT: COPD assessment text, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease. *$P \leq 0.05$ was significant

**Table 6:** The mean differences of FEF, FEV1, and CAT score before and after using of beta-blocker for Group 1

| Variable | Categories | *n* | Mean±SD | Paired *t*-test | *P* value |
|---|---|---|---|---|---|
| FEF | Before treatment | 18 | 56.22±14.38 | 4.165 | 0.001* |
| | After treatment | 18 | 52.89±12.89 | | |
| FEV1 | Before treatment | 18 | 68.83±12.81 | 4.69 | <0.001* |
| | After treatment | 18 | 59.61±18.98 | | |
| CAT score | Before treatment | 18 | 16.27±7.13 | −6.911 | <0.001* |
| | After treatment | 18 | 23.22±4.89 | | |

FEF: Forced expiratory flow, FEV1: Forced expiratory volume in 1 second, CAT: COPD assessment text, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease. *$P \leq 0.05$ was significant

**Table 7:** The mean differences of FEF, FEV1, and CAT score before and after using of beta-blocker for Group 2

| Variable | Categories | *n* | Mean±SD | Paired *t*-test | *P* value |
|---|---|---|---|---|---|
| FEF | Before treatment | 14 | 62.86±12.24 | 3.464 | 0.004* |
| | After treatment | 14 | 58.43±9.75 | | |
| FEV1 | Before treatment | 14 | 70.28±11.11 | 1.558 | 0.143 |
| | After treatment | 14 | 68.28±14.21 | | |
| CAT score | Before treatment | 14 | 17.35±7.55 | −1.434 | 0.175 |
| | After treatment | 14 | 19.35±5.65 | | |

FEF: Forced expiratory flow, FEV1: Forced expiratory volume in 1 second, CAT: COPD assessment text, SD: Standard deviation, COPD: Chronic obstructive pulmonary disease. *$P \leq 0.05$ was significant

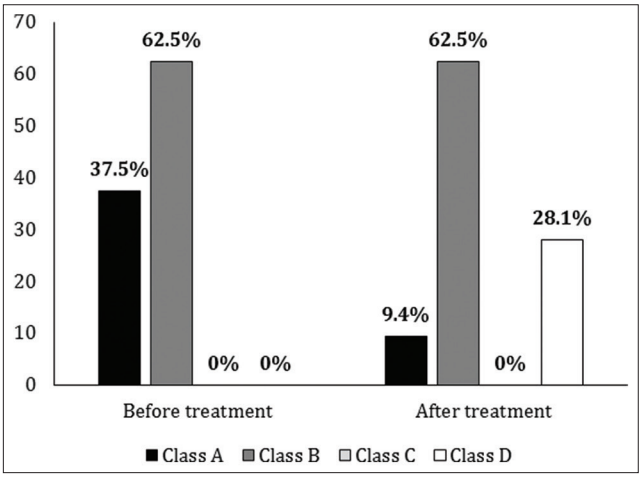


**Figure 1:** Distribution of all patients according to class before and after using of beta-blocker

Tobacco smoking is the most important risk factor for COPD. While in non-smoker patients, exposures to exhausts of fuel combustion have been identified one of the important factors. Other important risk factors associated with COPD are male sex; advancing age; lower socioeconomic status; outdoor air pollution in case of urban residence; repeated respiratory infections; and malnutrition.[13]

The overall exacerbation is seen in 28% of all patients but only 1 patient need hospitalization which indicates increase in exacerbation rate with the BB use but not to the serious level that needs hospitalization and these findings are not consistent with the usual concepts of BB safety in COPD may be due to small sample size and different grade of the disease severity. The change in the response to bronchodilator is seen in 18% only, and this finding is variable due to the subjectivity in the patient feeling and the other factors variable that may play a role even the patient psychological state.

In this study, there was no significant association between study groups and study variables mean that the 2 groups have the same characters for comparing and show the same events in the follow-up regarding the exacerbation, hospitalization, and change in the bronchodilator response.

About (28.1%) of patients change to Class D after using of 3rd generation BB. There were significant differences between means of FEF, FEV1, and CAT score before and after using of 3rd generation BB. This was expected as there is deterioration in with the use of a respiratory depressor drug in patients with respiratory disease.

About (38.8%) of patients change to Class D after using of 3rd generation BB in Group 1 while only (14.3%) of patients change to Class D after using of 3rd generation BB in Group 2. This again means that the patients with high reversibility percent show more tendency to have a more severe grade when exposed to 3rd generation BB.

### Limitation of the Study

1. No head to head comparing between third and other generations BB
2. No ability to use other parameters as lung volumes or diffusion capacity
3. Relatively small sample size and short duration of follow-up.

## CONCLUSION

Still, there are concerns when used BB the COPD patients even the 3rd generation type. The detrimental effects are shown more on patients with a high percent of reversibility mainly on FEV1 and CAT score. The patients with a high percent of reversibility show more tendency to have an exacerbation and be in more severe grade when use BB than those with low reversibility percent, so the reversibility percent can be used as an indicator for the bad effect of BB on COPD patients. This study recommends to find indicators for the detrimental effects of BB in COPD patients. Take caution in using BB in COPD patients with high reversibility percent. Further studies are required to clarify these findings.

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