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## **Cardiopulmonary interactions with beta-blockers and inhaled therapy in COPD**

<sup>1</sup>Sunny Jabbal Mb ChB, <sup>1</sup>William Anderson MD, <sup>1</sup>Philip Short MD, <sup>1</sup>Ashley Morrison BScN,  
<sup>1</sup>Arvind Manoharan Mb ChB, <sup>1</sup>Brian J. Lipworth MD.

*<sup>1</sup>Scottish Centre for Respiratory Research, Division of Molecular and Clinical Medicine,  
Ninewells Hospital and Medical School, Dundee, Scotland, DD1 9SY, UK*

**Address for Correspondence:** Dr BJ Lipworth, Scottish Centre for Respiratory Research,  
Division of Molecular and Clinical Medicine, Ninewells Hospital and Medical School,  
Dundee, Scotland, DD1 9SY, UK Tel: +44 (0)1382 383188 [b.j.lipworth@dundee.ac.uk](mailto:b.j.lipworth@dundee.ac.uk)

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## **Abstract**

Background: Beta-blockers remain underused in patients with COPD and cardiovascular disease.

Aim: We compared how different inhaled therapies affect tolerability of bisoprolol and carvedilol in moderate to severe COPD.

Design: A randomized, open label, cross-over study.

Methods: We compared the cardiopulmonary interactions of bisoprolol 5mg qd or carvedilol 12.5 mg bid for 6 weeks in conjunction with: (a) triple: inhaled corticosteroid /long acting beta-agonist/long acting muscarinic antagonist (ICS+LABA+LAMA), (b) dual: ICS+LABA, (c) ICS alone.

Results: 18 patients completed, all ex-smokers, mean age 65 years, forced expiratory volume in 1 second (FEV1) 52% predicted. Bisoprolol and carvedilol produced comparable significant reduction in resting and exercise heart rate. FEV1, forced vital capacity (FVC) and lung compliance (AX) were significantly lower with carvedilol vs bisoprolol while taking concomitant ICS/LABA ( $P < 0.05$ ) but not ICS/LABA/LAMA.

Conclusions: In summary, bisoprolol was better tolerated than carvedilol on pulmonary function at doses which produced equivalent cardiac beta-1 blockade. Worsening of pulmonary function with carvedilol was mitigated by concomitant inhaled LAMA (tiotropium) with LABA (formoterol), but not LABA alone.

. Registered at [clinicaltrials.gov](https://clinicaltrials.gov): NCT01656005.

## Introduction

Beta-adrenoceptor ( $\beta$ -ADR) antagonists are indicated in guidelines for the treatment of heart failure and post myocardial infarction (1). There is a reticence to use beta-adrenoceptor antagonists in patients with COPD, as they are perceived as contraindicated (2). So called cardioselective antagonists such as bisoprolol have a 14 fold higher affinity for  $\beta_1$  than  $\beta_2$ -ADR, while non selective antagonists such as carvedilol have a much higher relative affinity for  $\beta_2$ -ADR(3). In heart failure, 40% of cardiac  $\beta$ -ADR are of the  $\beta_2$  subtype due to a relative downregulation of cardiac  $\beta_1$ ADR from increased sympathetic drive (4). Hence one might postulate that preferentially blocking only  $\beta_1$ -ADR might not be as effective as blocking both subtypes. In one study comparing carvedilol and metoprolol in heart failure with reduced ejection fraction, the former was associated with 17% lower mortality, with similar reductions in heart rate(5). Metoprolol is less selective than bisoprolol with a 2 fold higher affinity for  $\beta_1/\beta_2$ -ADR(3).

The presence of  $\beta_2$ ADR antagonism may result in bronchoconstriction. Management guidelines clearly reinforce the use of cardioselective beta-blockers in patients with heart failure and chronic obstructive pulmonary disease (COPD) (6, 7). Despite this, lower prescribing rates for beta-blockers have been described in COPD patients with heart failure or post myocardial infarction (2, 8-10). In a meta-analysis of 15 retrospective studies in 21,596 patients with COPD the pooled estimate for mortality reduction with beta-blockers was 28% and for exacerbations was 38% (11). Among patients with known coronary arterial disease the mortality reduction was 39% and in heart failure was 26%. However, it remains unclear if beta-blockers may reduce exacerbations or mortality in individuals with COPD who have *covert* (untreated or unrecognized) cardiovascular disease (12). Prior to assessing this, which would require a longer study, a prospective trial is required to address concerns over potential beta blocker induced bronchoconstriction.

We performed a study comparing two commonly used selective and non-selective beta blockers, evaluating cardiopulmonary outcomes. This was in patients with moderate to severe COPD using realistic doses of bisoprolol 5mg qd and carvedilol 12.5mg bid, the most commonly tolerated doses in real life older populations (13). We have for the first time compared these beta-blockers in terms of their potential interactions with COPD therapy, namely inhaled long acting beta-agonist (LABA: formoterol, 24 micrograms), long acting muscarinic antagonist (LAMA: tiotropium 18 micrograms) and inhaled corticosteroid (ICS: beclometasone dipropionate, 400 micrograms).

The beta-blockers were given in combination with sequential step down inhaled therapy: starting with ICS/LABA/LAMA, ICS/LABA and finally ICS alone – this sequence allowed us to dissect out the respective interactions between beta-blockers with LAMA (i.e. ICS/LABA/LAMA vs ICS/LABA) and LABA (i.e. ICS/LABA vs ICS). It should be noted that whilst ICS only therapy is not licensed in COPD, in real life 8% of patients are taking such treatment (14).

A unique feature of our study was to use impulse oscillometry (IOS) to measure frequency dependent lung resistance (R) and compliance (as its reciprocal reactance: X). IOS is thought to be more sensitive than measuring forced expiratory lung volumes and flow rates using spirometry in order to detect subtle differences in airway constriction or dilatation (15).

## Patients and Methods

This study was registered at [clinicaltrials.gov](https://clinicaltrials.gov) under NCT01656005, and had favourable opinion from the East of Scotland Research and Ethics Committee (12/ES/0054). Patients attended the Scottish Centre for Respiratory Research, Ninewells Hospital, Dundee, Scotland, for their visits. Patients aged 40-80 with moderate to severe stable COPD, GOLD stages 2 and 3 (7), were initially screened, with FEV1 30-80% predicted, FEV1/FVC ratio <0.70 smoking history of >10 pack years, and oxygen saturation  $\geq$ 92% on room air, in sinus rhythm. Patients must not have had an exacerbation receiving oral corticosteroids within the past 3 months. Patients were excluded if they had a history of uncontrolled hypertension or heart

failure (NHYA class III-IV). Short acting beta-2-agonist use (salbutamol) was allowed during the study, but patients withheld 6 hours prior to any visit.

Visits were done from 8am-10am. Measures at each visit comprised impulse oscillometry (Jaeger Masterscreen IOS, Hochberg, Germany) including total lung resistance at 5Hz (R5) and central resistance at 20Hz (R20), lung compliance (as its reciprocal reactance X) at 5Hz (X5), area under the reactance curve (AX) between 5Hz and the resonant frequency; Spirometry was performed to British Thoracic Society standards (SuperSpiro, Micro Medical Ltd, Chatham, Kent, United Kingdom), including forced expiratory volume in 1s (FEV1), forced vital capacity (FVC) and relaxed vital capacity (RVC). St George's respiratory questionnaire (SGRQ) for health status and transition dyspnoea index (TDI) were also recorded. A 6-min walk test (6MWT) was performed (16) with heart rate, blood pressure, oxygen saturation (SpO2) and modified Borg scale for dyspnoea and fatigue, all being recorded pre and post exercise. Blood was taken for potassium, eosinophils, and N-terminal pro-BNP.

A randomized cross-over open label design was employed (Figure 1) comprising eight visits where patients received 6 weeks either carvedilol or bisoprolol. There was a 2 week washout between treatment period one and two, to ensure at least 5 half-life washout between beta-blockers. The order of randomization was performed to GCP standard by the Clinical Trials Pharmacy at Ninewells Hospital.

#### Data Analysis:

The study was powered on IOS at >80% to detect a 0.2 kPa/L.s difference in R5 with an SD of 0.23 kPa/L.s requiring a sample size of 18 completed patients per protocol using a cross-over design and alpha error of 0.05 (two-tailed). The data were checked for normality of distribution prior to analysis. Baseline values after run-in and washout were compared; having demonstrated no significant differences for treatment or sequence, the pooled baseline

values were used for the purpose of subsequent comparisons with randomized treatments. Within and between treatment comparisons across visits were made by repeated measures analysis of variance (ANOVA) with time order effects assessed, and then where a significant difference was observed this was followed by post hoc pairwise testing with Bonferroni correction.

## **Results**

The participant flow for the trial is shown in the consort diagram (Figure 2).

The trial ended when 18 patients completed per protocol. 83% of patients were male, with a mean age of 65 years, all were ex-smokers, Caucasian, with a mean pack year history of 47; FEV1 52% predicted, FVC 93% predicted, FEV/FVC ratio 0.45. Sequential reversibility testing in FEV1 was 7% (100ml) after 15 min following 400ug salbutamol and 12% (180ml) after 45 min following 80ug of ipratropium. Mean NT pro-BNP levels were 308pg/ml (95%CI 194-445). Mean blood eosinophil count was 210 cells/ $\mu$ L.

### **Pulmonary function:**

Respective baseline pulmonary function values after run-in and washout (i.e. on ICS/LABA but no beta-blocker) were not significantly different (Table 1), justifying the use of a pooled baseline for comparisons with randomized treatments.

For AX values compared to baseline there was a significant within treatment difference with carvedilol in conjunction with ICS/LABA and ICS but not with ICS/LABA/LAMA (Figure 3) – i.e. higher AX values indicating reduced lung compliance. AX values were significantly lower with carvedilol comparing concomitant inhaled therapy with ICS/LABA/LAMA vs ICS/LABA or ICS. With bisoprolol, AX was significantly worse than baseline only with ICS, furthermore AX was significantly different comparing ICS/LABA vs ICS. There was a significant difference in AX and X5 comparing bisoprolol vs carvedilol while taking ICS/LABA but not ICS/LABA/LAMA (Figure 3 and Table 2). Furthermore, with carvedilol



there was a significant difference for AX between ICS/LABA/LAMA vs ICS/LABA. No differences were found in either R5 or R20.

A similar pattern occurred for FEV1 and FVC in terms of a significant difference between beta-blockers with ICS/LABA but not ICS/LABA/LAMA (Figure 3 and Table 2). With both beta-blockers, FEV1 and FVC were significantly different comparing ICS/LABA vs ICS only for carvedilol, FEV1 was a significant difference comparing ICS/LABA/LAMA vs ICS/LABA. The differences in FEV1 were above the minimal clinically important difference (MCID) of 100mls at trough (17).

Exercise (6-minute walk test: 6MWT):

Oxygen saturations did not change significantly with level of inhaled therapy for either beta blocker, either at rest or with exercise (Table 3). 6MWT distance was significantly lower with bisoprolol but not carvedilol compared to baseline, while no differences were found comparing beta-blockers on any of the inhaled therapies, and the changes were less than the minimally important difference of 30m(18) (Table 3). Modified Borg scale for dyspnoea and fatigue was greater after exercise, but this was less than the minimally important difference of 1.0 unit(17),there were no significant differences between beta-blockers (Table 3).Both beta-blockers produced a similar degree of heart rate reduction compared to baseline for pre and post exercise in the order of 20 beats per minute, irrespective of concomitant inhaled therapy (Table 3). Serum potassium levels were unchanged.

Health status and Dyspnoea index:

For health status as SGRQ (Table 3) there were no significant changes from baseline and no differences between beta-blockers, with reference to a minimal important difference of 4 units(17).

The mean transition dyspnoea index (TDI) values were not significantly different between beta-blockers on any of the inhaled treatments. Values for both beta-blockers were lower on

ICS vs ICS/LABA (Table 3), while for bisoprolol values were also lower on ICS/LABA vs ICS/LABA/LAMA. Changes in TDI were less than the minimal important difference of 1.0 unit(17).

## **Discussion**

The results of the present study revealed some important new findings regarding beta-blockers and their interaction with long acting bronchodilators in patients with moderate to severe COPD. The addition of tiotropium as in combination with formoterol as inhaled triple therapy, resulted in unchanged pulmonary function values compared to baseline, while taking carvedilol or bisoprolol. Normally stimulation of inhibitory pre-junctional beta-2 receptors acts as a brake to post junctional cholinergic transmission (19). The presence of beta-2 receptor blockade would increase acetylcholine release which stimulates post junctional M3 receptors to produce constriction of airway smooth muscle. Hence we speculate that tiotropium conferred protection against bronchoconstriction due to beta-2 receptor blockade with carvedilol. The same bronchoprotective effect of tiotropium with ICS has also been reported in asthmatic patients taking propranolol (20).

When the LAMA was stopped and patients subsequently continued on ICS/LABA, the protective effect of tiotropium became evident as worsening of pulmonary function with carvedilol but not bisoprolol. A significant difference between beta-blockers was seen for spirometry (FEV1, FVC) and IOS (AX, X5) while taking ICS/LABA, which for FEV1 exceeded the MCID of 100ml In this case, carvedilol negated the inhibitory effect of formoterol on pre-junctional beta2 receptors but without any accompanying post junctional M3 receptor antagonism. Post junctional beta-2 receptor stimulation by formoterol which normally produces bronchodilation, was also antagonised by carvedilol. However, pulmonary function was no worse with bisoprolol due to a negligible degree of beta-2 blockade associated with the 5mg dose due to its 14/1  $\beta$  1/2 selectivity ratio (3, 21).

When patients then stopped LABA and continued on ICS alone, there was as expected further decline in pulmonary function with both beta-blockers due to the absence of formoterol

induced bronchodilation as well as antagonism of circulating adrenaline. The clinical implication is that patients with COPD requiring beta-blockers should be prescribed concomitant LAMA to protect against potential bronchoconstriction, especially if using a non selective drug. As selective beta-blockers exhibit dose related beta-2 receptor antagonism(22, 23) the concomitant use of LAMA may also be advocated when using at higher doses of bisoprolol.(21) The likelihood is that most patients with COPD will already be taking a LAMA as current guidelines recommend the use of LAMA across GOLD stages 2-4, as they reduce exacerbations and improve quality of life (24). Moreover, in a retrospective study of 2853 COPD patients over 4-7 years, adding tiotropium to ICS/LABA was found to reduce respiratory and cardiovascular mortality (25).

Our results showed that both beta-blockers exhibited a comparable degree of heart rate reduction at both rest and after exercise, which in turn infers that bisoprolol 5mg qd and carvedilol 12.5 bid exhibited a similar degree of cardiac beta-1 blockade with a mean fall in the order of 20 beats per minute - a clinically meaningful response(26). We chose these pragmatic doses, for our COPD patients, as we considered that higher doses might not be tolerated in terms of symptomatic bradycardia and hypotension in a cohort of susceptible elderly patients (13). The observation of lowering of SBP and DBP with bisoprolol but not carvedilol was perhaps surprising given that carvedilol produces peripheral vasodilatation due to alpha-1 receptor blockade. However, at the same time the greater beta-2 receptor antagonism with carvedilol would attenuate vasodilatation due to stimulation of peripheral arterial beta-2 receptors(26).

As our patients did not have heart failure we are unable to draw any meaningful conclusions with regards to the relative efficacy of these beta-blockers on cardiac function. In this regard it is conceivable that haemodynamic responses to beta-blockade might have been altered in heart failure patients. Although none of our patients were being treated for heart failure, we acknowledge that an echocardiogram would be required to diagnose cases of covert heart failure. For example, in a comparison of carvedilol and bisoprolol in 883 elderly patients

with heart failure over 12 weeks, both drugs produced comparable reductions in blood pressure and improvements in ejection fraction (13).

Jabbour et al also reported a significantly lower heart rate on carvedilol than bisoprolol amounting to 4 beats/min, whereas in our study we observed no such difference in chronotropic reduction. This discrepancy between the two studies may be explained by the presence of heart failure where the negative chronotropic effect of carvedilol might be enhanced due to a relatively higher proportion of cardiac beta-2 receptors. Our patients had a mean N-terminal pro-BNP level of 308 pg/ml. This has been described as the grey zone in COPD patients where they may be pulmonary arterial pressure overload and right ventricular wall stress (27)..

The duration of treatment in each inhaler arm was of sufficient duration to achieve steady state effects in terms of potential pharmacodynamic interactions on both airway beta-2 and M3 receptors. One could argue that the step-down phase from ICS/LABA to ICS alone is not clinically relevant as the latter are not licensed in COPD. However, this allowed us to dissect out the effect of LABA by comparing ICS alone to prior ICS/LABA.

One unique aspect of our study was the use of IOS which is more sensitive than spirometry in detecting subtle changes in lung physiology. Unlike spirometry which measures lung volumes and flow, IOS measures lung resistance (R) and compliance (X) and is also able to differentiate between central and peripheral airways by looking at their frequency dependence, with lower frequencies reflecting changes in smaller airways.(28) Our study was powered on total airway resistance (R5) which did not detect any significant effects of beta-blockade. Furthermore, there was no significant change in central (R20) or peripheral airway resistance (R5-R20). In contrast, there was a significant change in AX which reflects peripheral airways compliance, as the area under the reactance curve between 5Hz and the resonant frequency. This showed reduced lung compliance (as higher reactance: AX) for carvedilol versus bisoprolol in conjunction with either ICS/LABA or ICS alone.

The relative sensitivity of spirometry and IOS can be seen as a 9% versus 28% change in FEV1 and AX respectively for ICS/LABA with carvedilol as change from baseline. The present findings comparing the relative effects of carvedilol on spirometry and IOS in COPD are similar to those previously reported in asthma with propranolol.(15)

The significant differences observed between beta-blockers on pulmonary function were not associated with commensurate differences on Borg scale (dyspnoea or fatigue), health status (SGRQ) or transition dyspnoea score (TDI). Bisoprolol with ICS significantly lowered 6MW distance compared to baseline by 26 metres, while the biggest difference between beta-blockers was 19 metres, both of which are less than the minimal important difference of 30m (18).

In summary, bisoprolol was better tolerated than carvedilol on pulmonary function at doses which produced equivalent cardiac beta-1 blockade. Worsening of pulmonary function with carvedilol was mitigated by concomitant inhaled tiotropium with formoterol, but not formoterol alone.

Further prospective long-term studies are warranted to compare bisoprolol and carvedilol in patients with heart failure and COPD to look at their relative effects on exacerbations and mortality.

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**Figure Legend:**

Figure 1.

Flow chart for study protocol. BDP/FF: Beclometasone dipropionate 100µg/formoterol fumarate 6µg, 2 puffs twice daily; BDP: Beclometasone dipropionate 200µg 2 puffs twice daily.

Figure 2.

Consort diagram showing participant flow

Figure 3.

Effects of bisoprolol and carvedilol on expiratory lung volume (FEV1) (top) and compliance (as reactance area: AX) (bottom), stratified according to sequential inhaled therapy. Asterisk denotes significant difference within each beta-blocker from baseline ( $P < 0.05$ ), Cross denotes significant difference between beta-blockers ( $P < 0.05$ ).