To β-Block or Not to β-Block: That Is Still the Question in Chronic Obstructive Pulmonary Disease

Robert J. Hancox, M.D.

Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand

ORCID ID: 0000-0002-3922-7144 (R.J.H.).

Managing cardiac disease in patients with chronic obstructive pulmonary disease (COPD) presents a dilemma. On the one hand, we know that patients with COPD have a high risk of adverse cardiac outcomes: especially in the context of an exacerbation (1, 2). These are outcomes and risks that would be managed with β-blockers in other patients. On the other hand, respiratory physicians have traditionally avoided β-blockers in patients with airway disease because of the concern that they may cause bronchospasm and block the therapeutic effects of β_2-agonists. Although COPD guidelines now suggest that cardioselective β-blockers may be used in COPD for patients with cardiovascular indications (3), they are still underused, suggesting that many clinicians remain wary (4, 5).

Cardioselective β-blockers, which have a higher affinity for β_1- than β_2-receptors, should be safer in COPD, and most observational studies have been reassuring (6–8). Indeed, some observational research suggests that cardioselective β-blockers may even improve outcomes in COPD (9).

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However, until recently, there were no large-scale randomized-controlled trials to investigate this possibility, and most studies of β-blockers for cardiovascular disease have excluded patients with airway disease.

BLOCK COPD was the first trial to be planned with sufficient power to address the question of whether cardioselective β-blockers are beneficial or harmful in patients with COPD (10). The study was designed to test the hypothesis that metoprolol would reduce the frequency of COPD exacerbations. Unfortunately, the trial was stopped after just over half of the target number of participants was recruited. This was partly because of futility when interim analyses indicated that the full sample would be unable to show a difference between metoprolol and placebo. However, there was also a safety concern: although there was no apparent difference in the overall rate of exacerbations (the primary outcome), there were higher rates of severe and very severe exacerbations in the metoprolol group (rate ratios, 1.51 [95% confidence interval (CI), 1.00–2.29] and 3.71 [95% CI, 1.10–16.98], respectively). The metoprolol group also had worse COPD control as measured by the COPD Assessment Test and the San Diego Shortness of Breath Questionnaire.

What are clinicians to make of this? Why would there be the same rate of exacerbations but more severe exacerbations with metoprolol? Of course, this may have been a chance finding among one of many secondary outcomes, but it raises a safety concern that we cannot ignore. What mechanism might explain this outcome, and can we predict who is most at risk with a β-blocker? The original paper was unable to identify subgroups of participants at greater risk on the basis of a wide range of attributes, so in the meantime, we have to regard all patients with COPD as potentially at higher risk of severe exacerbations if we start a β-blocker.

In this issue of *AnnalsATS*, Parekh and colleagues (pp. 1642–1649) provide important new data from the BLOCK COPD trial on the effect of metoprolol on lung function and whether changes in lung function predicted severe exacerbations (11). Metoprolol induced small falls in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) over the first 28 days when compared with placebo (approximately 25 ml for FEV_1 and 80 ml for FVC at Day 28: for FEV_1 the difference was only statistically significant when analyzed on a log-scale). Cardioselective β-blockers have previously been reported to cause small initial reductions in lung function in patients with airway disease, usually followed by recovery to baseline (12). Although the declines in lung function in the BLOCK COPD trial were no longer statistically significant by the end of the study, they were consistently greater in the metoprolol group than in the placebo group, suggesting that some β-blocker impairment of lung function may persist. The changes in lung function did not predict exacerbations, however. Exacerbations were more common among those with greater FVC responsiveness to albuterol at baseline, but this was not different between those treated with metoprolol or placebo.

How should clinicians use this new information? Is this small, and perhaps temporary, fall in lung function a cause for concern? Although the decline in lung function was less than would usually be regarded as clinically important, this observation demonstrates that metoprolol has a definite, albeit small, adverse effect on airway caliber at therapeutic doses, which is almost certainly because of partial blockade of β_2-receptors. Could this explain the higher rate of severe exacerbations? We can only speculate, but it seems plausible that this small degree of β-blockade might lead

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to a diminished response to inhaled β_2-agonists. Most studies have not found a significant reduction in β-agonist responsiveness during treatment with cardioselective β-blockers (6), but a diminished response to β-agonists tends to be more obvious when there is increased airway smooth muscle tone, such as during exacerbations (13). Exacerbations are usually caused by infections, and there is no reason to expect these to happen more often among those taking a β-blocker. The severity of an exacerbation, however, is defined by the treatment required. Could a reduced or slower response to emergency β_2-agonists among those taking metoprolol lead to an escalation to a higher level of therapy and thereby meeting the definition of a severe exacerbation? In other words, would a patient with a moderate exacerbation in the emergency department who was slow to respond to bronchodilator treatment be more likely to be admitted to the hospital?

Where do we go next with this clinical dilemma? These findings show that despite being relatively "cardioselective", metoprolol does block airway β_2-receptors. The affinity of current blockers for β_1- versus β_2-receptors is on a spectrum (14): it is likely that an agent with greater selectivity would avoid the adverse effects seen with metoprolol in the BLOCK COPD trial. There are at least two ongoing clinical trials of β-blockers in COPD that may answer this (15, 16). Both are using bisoprolol, which appears to have higher β_1 selectivity than metoprolol (14). Both studies have faced considerable challenges during the coronavirus disease (COVID-19) pandemic, but it is hoped that they will provide sufficient data to resolve the issue of safety.

In the meantime, clinicians have few data to guide them. Many patients have clear cardiac indications for β-blocker treatment, but it is difficult to predict the balance of risks and benefits for some patients. The BLOCK COPD trial excluded patients with a proven cardiac indication for a β-blocker and, therefore, it is not surprising that no cardiac benefits were observed. Until we have more data, clinicians will need to balance the likely cardiac benefits from cardioselective β-blocker treatment with the observed increased risk of a severe COPD exacerbation. The article by Parekh and colleagues shows that monitoring the lung function response to β-blockers is unlikely to help. Patients should be informed of the risks and involved in the decision. If it is decided to start a β-blocker, it seems sensible to use the most cardioselective β-blocker available. ■

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