Beta-blockers and COPD: the show must go on

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Current evidence on beta-blockers efficacy and safety in COPD is encouraging but limited with future studies needed http://ow.ly/IaNL301YANI

Identification of comorbidities is now recognised as one of the pillars for a comprehensive clinical evaluation in chronic obstructive pulmonary disease (COPD) [1]. Specifically, the burden of coexisting cardiovascular disease in COPD has gained significant attention, with specific algorithms being developed for its clinical detection [2]. The relationship between the heart and COPD is of clinical relevance not only for the well-documented relationship between the two organs [3], but also for the potential mutual influence of treatments. The interactions between oral beta-blockers and inhaled β-adrenergic drugs pose significant challenges for clinicians involved in the management of patients with chronic cardiorespiratory conditions. In particular, the use of beta-blockers in COPD remains the subject of ongoing controversy [4].

In this issue of the *European Respiratory Journal*, Lipworth *et al.* [5] provide a comprehensive summary on the use of beta-blockers in patients with COPD. In their narrative review, the authors disentangled the complex links between COPD and the heart, reviewed the available data on the use of beta-blockers for reducing exacerbations and mortality, and summarised the unmet needs in the field, with special reference to a more in-depth knowledge of how different beta-blockers can affect pulmonary function based on their pharmacology. Despite published reports of physicians being reluctant to prescribe beta-blockers in COPD patients with a history of myocardial infarction or coexisting heart failure, the authors conclude that there are compelling reasons for the use of cardioselective beta-blockers in this patient group.

In order to understand the potential implications of beta-blockers on COPD a brief review of the lung innervation and anatomical distribution of receptors in the lung is required. In humans, the direct sympathetic innervation of the airway smooth muscle is very poor [6]. Somewhat counterintuitively, however, the density of β-adrenergic receptors is markedly high and their expression can be identified in different cell types. In the human lung, β-adrenergic receptors on smooth muscle, epithelial and mast cells are of the β_2-subtype, whose density increases towards the peripheral airways. By contrast, human submucosal glands and alveolar wall cells also express β_1-receptors [7, 8]. In the healthy heart, β_1- and β_2-adrenergic receptors coexist in a 4:1 ratio. However, in the failing heart, β_1-adrenergic receptor numbers decrease, paralleled by an increase in β_2-adrenergic receptors, ultimately resulting in a 3:2 ratio [9]. In this scenario, the occurrence of interactions may not be negligible. In general, the effects of drugs that act on adrenergic receptors depend both on the intrinsic pharmacological properties of the drug (including the β_1/β_2 ratio) and its bioavailability (intended to be high in systemic beta-blockers but low in inhaled β-agonists with an adequate inhalation technique).

Starting from these premises, multiple evidence excellently summarised by Lipworth *et al.* [5] merits comment. First, a point that is worth considering is the potential effect of beta-blockers in the prevention

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of exacerbations in stable COPD patients. The main difficulty in the interpretation of the available data is that the published reports are mainly retrospective analyses of clinical records. It is well-known that these studies are not only limited by potential biases and confounders that were not taken into account but also influenced by the analytical approach used. Additionally, the identification of COPD cases and COPD exacerbations in clinical records has been questioned [10]. The discrimination between a COPD exacerbation and a decompensation of coexisting cardiac or respiratory diseases may be problematic in daily clinical practice. The problem is obviously even more difficult when clinical datasets are retrospectively reviewed. It should also be kept in mind that a worsening of respiratory symptoms in a COPD patient does not invariably reflect a COPD exacerbation [11]. Accordingly, use of the term complications rather than exacerbations has been proposed [12]. Strict diagnostic algorithms have been proposed for the adequate identification and analysis of stable [13] and exacerbated COPD patients in clinical records from primary [14] and secondary care [15].

Interestingly, one prospective study conducted in the COPDGene cohort assessed whether the use of beta-blockers can decrease the occurrence of exacerbations [16]. The results of this longitudinal study indicated that the use of beta-blockers was associated with a significant reduction in COPD exacerbations, independent of the severity of airflow obstruction. A cross-sectional study of COPD patients with chronic heart failure or coronary artery disease reported similar findings [17]. It should be noted, however, that another study found opposite results in patients in Global Initiative for Chronic Obstructive Lung Disease stages 3 and 4 on home oxygen therapy [18]. To make things more complex, different small studies have shown a decrease in different lung function parameters with the use of the cardioselective beta-blocker bisoprolol [19, 20]. Therefore, the question as to whether beta-blockers may decrease lung function while reducing the frequency of exacerbations remains open and researchers should consider whether we are seeing an effect on COPD exacerbations or on cardiac events. Taken together, there is retrospective and some longitudinal evidence that beta-blockers can decrease acute adverse clinical events in COPD patients. Further research efforts are needed to dissect the exact impact of beta-blockers on COPD exacerbations, respiratory symptoms and lung function parameters. The βLOCK COPD (β-blockers for the prevention of acute exacerbations of chronic obstructive pulmonary disease) trial is currently being conducted and its results will surely shed more light on this issue [21].

Second, another source of controversy is the potential prognostic significance of beta-blocker use in patients with COPD. Beside the abovementioned issue related to exacerbations, the effect of beta-blockers on cardiac function should be considered separately in patients with and without COPD. A number of studies have investigated the impact of COPD on cardiac function. Patients with COPD but no overt cardiovascular disease show signs of left ventricle concentric remodelling [3]. Moreover, COPD has emerged as a significant risk factor for ventricular arrhythmias and sudden cardiac death [22]. Nonetheless, it remains unclear whether the cardiac effect of beta-blockers may differ in patients with COPD compared with those without. Consequently, it is still debatable whether beta-blockers reduce the risk in COPD only through their cardiovascular effects or due to a potential respiratory effect and, if this is so, by which mechanism. Interestingly, the prospective COPDGene study failed to identify a statistically significant association between the use of beta-blockers and mortality in COPD [16]. This relationship needs to be prospectively evaluated in longitudinal trials with rigorously established clinical end-points.

Third, the potential usefulness of beta-blockers during COPD exacerbations merits consideration. Studies based on the analysis of clinical datasets suggest that the use of beta-blockers in patients admitted for a COPD exacerbation is significantly associated with a reduced mortality [23]. Beside the abovementioned issue related to the retrospective identification of exacerbations, the diagnosis of an exacerbation represents another challenge. The European COPD Audit revealed that 40.6% of patients admitted to hospital and subsequently discharged with a diagnosis of a COPD exacerbation did not have a previous diagnosis of COPD according to current guidelines. In addition, 12.9% of these subjects had previously undergone spirometry that did not reveal obstructive findings [24]. In real-world practice, several patients with COPD require hospital admission because of cardiac disorders. The cardiovascular risk of COPD patients is also markedly higher during exacerbations, which are accompanied by increased levels of biomarkers of cardiac injury [25] and carry negative prognostic implications [26, 27]. Beta-blockers may limit these phenomena and improve survival in patients admitted for exacerbations [23]. Again, further research is needed to investigate whether the positive impact of beta-blockers should be attributed to their effect on cardiac function and/or respiratory exacerbations *per se*.

Another point examined by Lipworth *et al.* [5] is the potential crossover efficacy between systemic beta-blockers and inhaled medications. Pharmacological treatment of COPD exerts beneficial effects on both cardiac function and lung vasculature, which may in turn contribute to the favourable effects of inhaled therapies [28]. Even at low doses, the β_1-selective antagonist atenolol may protect against the chronotropic, inotropic and electrocardiographic effects of inhaled β-agonists [29]. Furthermore, the

administration of beta-blockers in a murine model of asthma resulted in an increased pulmonary β-receptor density and moderate anti-inflammatory effects [30, 31], suggesting that this drug class may increase the response to inhaled asthma medications. Another interesting observation is that long-acting muscarinic antagonists can reduce the risk of bronchoconstriction even when nonselective beta-blockers are used in patients with asthma [32]. If similar results are reported for patients with COPD, future trials specifically focusing on this new efficacy end-point will be needed.

Finally, Lipworth *et al.* [5] correctly point out that the presence of untreated or undetected cardiovascular disease may influence both the clinical presentation and outcomes of COPD. Patients with silent cardiovascular disease may specifically represent a significant clinical challenge because they may be under-recognised. In addition, the acquisition of echocardiography images may be problematic owing to lung hyperinflation. The development of a standardised diagnostic work-up for the detection of cardiovascular disease in patients with COPD may be helpful to reduce the risk of underdiagnosis.

In summary, most of the available evidence indicates that beta-blockers are generally safe in COPD patients. Nonetheless, additional longitudinal studies are needed before more definitive recommendations can be made. Continuing research into the complex relationships of beta-blockers in COPD will be obviously required. All we can say, in remembrance of Queen's international hit from the "Innuendo" album (released in October 1991), is that "the show must go on" in the field. Future points that specifically need to be clarified include: 1) standardisation of the diagnostic approach for the detection of cardiac dysfunction in COPD; 2) the safety of beta-blockers in COPD, with a special focus on the differences between distinct molecules; and 3) the effect of beta-blockers in terms of exacerbations, symptoms, lung function parameters and prognosis. With these data to hand, the prescription of beta-blockers to COPD patients will take place with a reasonable degree of confidence.

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