Is the Use of β -Blockers in COPD Still an Unresolved Dilemma?

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Key Words

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Abstract

β -Blockers are competitive antagonists at β -adrenergic receptors (β -AR) and are a life-saving form of treatment in different cardiovascular diseases (CVD). Despite current guidelines supporting the use of selective β_1 -blockers in patients with CVD and especially in heart failure (HF), they are still largely underused, mostly as a consequence of the presence of chronic obstructive pulmonary disease (COPD). In primary care, prevalence of COPD in patients with HF is approximately 25%, and it will rise in the next years. In the general population, only 20% of COPD patients with HF are treated with β -blockers. β -Blockers may result in pulmonary adverse effects that are relevant to COPD patients. Bronchoconstriction may be the consequence of: absence of cardioselectivity; loss of cardioselectivity at high doses, and unopposed stimulation of cholinergic muscarinic M_2 receptors. The concern of inducing bronchospasm is the more likely explanation of a poor prescription of β -blockers in patients with CVD also suffering from COPD. However, under carefully controlled conditions, which include close monitoring of lung function and appropriate selection of the drug and titration

of the dose on a case-by-case basis, selective β_1 -blockers can be safely administered to most patients with COPD. Pneumologists and cardiologists should develop a detailed and standardized protocol to guide the use of selective β_1 -blockers in everyday practice, which could significantly reduce the physicians' mistrust of β -blockers in COPD patients.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a very common smoking-related disease, characterized by persistent airway obstruction and increasing morbidity and mortality worldwide [1]. Patients with COPD also have coexisting cardiovascular co-morbidities [2] associated with COPD exposure to smoke and chronic inflammation, i.e. chronic heart failure (CHF), coronary artery disease (CAD) and hypertension.

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Cardiovascular diseases (CVD) are often the first or second cause of death in COPD patients, regardless of the severity of airway disease. Approximately one third of patients with COPD die of CVD [3–5], and COPD patients are at increased risk of death and hospitalization for CVD [6]. In patients hospitalized for heart failure (HF), COPD worsens the prognosis [7].

COPD prevalence in patients with CHF ranges from 23 to 33% [8–11], whereas about 25% of elderly patients with COPD have unrecognized CHF [6]. In the community, prevalence as well as incidence have increased in the last decade, both in men and women [11], and approximately two thirds of the patients with HF and COPD are current or previous smokers [11]. Retrospective analysis of health care data shows that the odds ratio of prevalence of congestive HF in COPD is 3.8 times that of similar age-matched non-COPD patients [6]. Elderly patients with clinical or functional diagnosis of COPD with concurrent, mostly left-sided, early-stage HF (in the general population half of the patients with CHF are aged >75 years) [12] had twice the risk of dying compared with COPD patients without HF [13]. COPD patients more frequently die of CVD [4], mainly as a consequence of CHF [14]. It should be noted that the 5-year survival rate in patients with COPD and HF is approximately 70–80% [13], suggesting that adequate treatment of HF changes the prognosis in COPD patients remarkably [8, 13]. However, from a therapeutic standpoint, the coexistence of COPD and CHF complicates HF treatment and is often responsible for suboptimal pharmacological intervention. Moreover, the higher mortality of patients with concomitant CHF and COPD has been linked to an under-use of recommended pharmacological treatment, such as β -blockers [15].

Indeed, the coexistence of COPD and CHF exposes patients to a double jeopardy. From a diagnostic point of view, CHF can remain misdiagnosed in COPD because the symptoms are similar and the increasing volumes associated with COPD hamper auscultation of cardiac tones. Furthermore, the acoustic window is frequently poor in COPD patients, thereby impeding evaluation of cardiac function by Doppler echocardiography [16]. The diagnosis and treatment of coexistent COPD and CHF is even more challenging, especially in the elderly, due either to their partial inability to perform pulmonary function tests and/or decreased accessibility of health resources. Indeed, the morbidity of patients with COPD and CHF will rise in the next years due to prolonged life expectancy, as both conditions become increasingly more prevalent with age. As the adjusted mortality rate for

COPD still rises and the mortality of patients with CHF remains stable, the importance of treating both conditions optimally has to be stressed.

CAD has been reported in 10 [17] to 20% of patients with COPD [18], whereas the prevalence of COPD in adults with systemic hypertension is similar to that in the general population (approximately 30%) [19].

The reason for the high coexistence of CVD and COPD is likely to be multifactorial. In general, the increased CVD risk is mostly related to excess adrenergic activity. High sympathetic activity and neurohormonal activity are linked to vascular and myocardial damage, left-ventricular hypertrophy and an increased risk of ischemic episodes [20]. The marked increase in peripheral sympathetic discharge and the increased plasma norepinephrine levels are further increased in the presence of COPD caused by hypoxia. A further increase in the sympathetic discharge may be due to intermittent nocturnal hypoxia in the presence of obstructive sleep apnea or central sleep apnea/Cheyne-Stokes respiration [20]. The progression of CVD in patients with COPD could be further accelerated by a low-grade systemic inflammation which determines coronary atherosclerosis, which ultimately results in ischemic cardiomyopathy.

Autoradiographic and radioligand binding studies have shown the co-existence of both β_1 - and β_2 -receptors in the human lung [21], bronchus and trachea [22]. β -Adrenergic receptors (β -AR) are unevenly distributed throughout the airways, with the highest receptor density in the lung and the lowest in the trachea [23]; receptor distribution and activity are often discrepant; β_2 -AR predominate in bronchial smooth muscles, whereas β_1 -AR account for 10 and 30% of β -receptors in submucosal glands and alveolar walls, respectively. β -AR (mainly the β_2 subtype) stimulation induces smooth muscle relaxation, clearance of alveolar fluid and changes in ion fluxes.

In the human heart, the β_1 -AR/ β_2 -AR ratio is about 70–80:30–20% (about 50–60:50–40% in HF) [24]; β -AR activation leads to an increase in the rate and force of myocardial contraction (positive inotropic and chronotropic effects) [24]. Norepinephrine has higher affinity for human cardiac β_1 -AR than β_2 -AR. In vascular smooth muscles, β_2 -AR are predominant and mediate vasodilatation. Their proportion changes depending on both the organ and the disease [25].

β -AR function is influenced by receptor density and affinity to G-proteins [23, 26]. In addition, basal signal response is mediated through β -AR but also through direct activation of adenyl cyclase. β -AR may exist in mul-

multiple active conformations, each of which could display a distinct signaling profile, and several polymorphisms of β -AR have been reported. The former may explain the differences in clinical effectiveness of different β -blockers and the latter the differences in responses in different patients [27].

Current international guidelines for CHF [12], CAD [28] and hypertension [29] support the benefit of the treatment with β -blockers in most patients, including COPD patients. Despite this, in selected populations, only 20–70% of COPD patients with CHF and myocardial infarction (MI) received β -blockers [11, 18, 30–33]. In the general population, approximately 20% of COPD patients and 40% of non-COPD patients were treated with β -blockers for CHF [11]. The under-use derives from the well-recognized capacity of non-cardioselective β -blockers to cause bronchoconstriction, which determines a widespread reluctant attitude toward their use in patients such as those suffering from asthma but also COPD [34].

Pharmacology of β -Blockers

β -Blockers are a heterogeneous class of drugs which act by inhibiting the adverse effects of sympathetic nervous system activation. Propranolol was synthesized about 60 years ago and was the prototype of β -blockers [35]. Since then many compounds have been developed. They are characterized by different pharmacokinetics and pharmacodynamic properties [36–40]. While the older agents have the same effect on β_1 - and β_2 -receptors, second-generation β -blockers have a higher affinity for β_1 -receptors. Practolol, the first β_1 -selective blocker, was introduced in the late 1960s. Subsequently, many other β_1 -selective blockers without toxicity were introduced in clinical practice. β_1 -Selective blockers have the advantage of a major interaction with cardiac β_1 -receptors, and less influence on bronchial tone and vessels. Thus these drugs are rather cardioselective but not cardiospecific. β_1 -Receptor selectivity may be a dose-dependent property [35, 36]; consequently, with increasing dose, β_1 -selectivity decreases.

Only few β -blockers can partially activate AR in the absence of endogenous catecholamines, e.g. pindolol and partially acebutolol. They possess a partial agonist activity. In the presence of catecholamines, β -blockers with intrinsic sympathomimetic activity (ISA), or partial agonist activity [25, 36], remain effective anti-hypertensive agents, and cause less slowing of heart rate at rest, less

depression of atrioventricular conduction and directly reduce peripheral vascular resistance. However, it is still debated whether β -blockers with ISA are an advantage or a disadvantage in cardiac therapy [35, 36]. Some investigators have made claims that ISA in β -blockers protects against myocardial depression and bronchial constriction. However, evidence supporting the latter claim is unconvincing, since they might potentially cause β_2 -AR downregulation [25].

Some β -blockers, e.g. labetalol and carvedilol, have antagonistic effects on both α - and β -AR and thus have vasodilating properties [35, 36]. The α -receptor-blocking property determines a reduction in peripheral vascular resistance and a better preservation of cardiac output compared to propranolol. Thus both drugs are useful in treating systemic hypertension and symptomatic congestive HF. Although the function and expression of α -receptors in the lung are poorly defined [41], α -receptor-blocking drugs might have a weak bronchodilating activity.

β -Blockers exert their activity by preventing agonist binding (neutral antagonists). However, some β -blockers such as nadolol, carvedilol, bisoprolol and metoprolol also reverse the constitutive activity of unbound β_2 -AR in the absence of agonist (inverse agonist). In contrast to β_2 -AR agonists which alter β_2 -AR such that the affinity for ligands is 10-fold reduced, with downregulation and desensitization of response, β -blockers do not provoke desensitization or alterations in receptor conformation. However, chronic long-term administration of β -blockers causes β -AR upregulation and increases their density [42]. Consequently, prior exposure to β_2 -AR agonists may reduce binding of antagonists to β -receptors. This may explain the high tolerance for β -blockers in COPD patients who routinely inhale β_2 -AR agonists.

Perioperative Use of β -Blockers in COPD

Current guidelines support a relatively wide indication for the perioperative use of β -blockers in patients undergoing major vascular surgery to reduce the incidence of peri- and postoperative cardiac complications, including sudden death, angina and MI [43]. Indeed, elevated levels of catecholamines during and after surgery are a well-known phenomenon, and in association with hormonal and blood rheology changes and the effects of anesthetics, catecholamines are the mechanisms responsible for cardiovascular complications [44].

In a cohort of selected, moderate-to-severe COPD patients, cardioselective β_1 -blockers are associated with reduced short- and long-term mortality in patients who underwent major cardiovascular surgery [45]. An overwhelming body of evidence suggests that perioperative β -AR blockade reduced the occurrence of morbidity related to cardiac complications [46–48], especially in patients at a very high risk of perioperative cardiovascular adverse events [49]. This risk is linked to the preexisting cardiovascular risk factors and to the risk of the procedure itself. The role of β -blockers in intermediate- and low-risk patients needs to be better defined. Thus the benefit of β -blocker treatment in COPD patients undergoing major surgery should be determined on an individual basis by balancing the risk/benefit ratio. Finally, their overall impact on patients undergoing non-cardiac surgery has been questioned [50].

β -Blockers in COPD and MI

American Heart Association and American College of Cardiology guidelines recommended initiating long-term β -blocker treatment in all MI patients [28]. The major convincing benefits have been documented in patients with MI, both before and after infarction [51, 52]. The beneficial effects of β -blockers in patients with COPD who had recently experienced MI have also been demonstrated: survival in patients with and without COPD is similar after MI [53, 54]. Randomized controlled studies show that mortality was reduced [55] by approximately 15–40% in COPD patients with coexisting CAD [56]. The effect was similar to that in patients without COPD [55] and possibly limited to patients who have preexisting cardiac disease [53].

β -Blockers in COPD and Hypertension

Historically, β -blockers are a major class of anti-hypertensives. Among COPD patients with hypertension, β -blockers monotherapy has been shown to reduce all-cause mortality compared to other anti-hypertensive drugs [57]. A recent meta-analysis evaluated the efficacy of β -blockers as first-line therapy for hypertension in preventing major cardiovascular outcomes such as non-fatal MI or stroke, or death. Data from randomized trials [58] showed that several β -blockers have similar efficacy in patients aged <60 years, while in older patients they were associated with a higher risk of cardiovascular events.

Since β -blockers are not the first-line treatment for hypertension [29], there is no need to use them in COPD patients with hypertension. Thus it could be suggested that β -blockers must be stopped in these patients and even cardioselective β_1 -blockers must be substituted. Indeed, with several classes of drugs available to treat hypertension, the mandatory use of β_1 -blockers to treat hypertension in COPD patients became unlikely, with the possible exception of severe hypertension. Although the likelihood of adverse events to all other classes of anti-hypertensive drugs is extremely low, in this case a trial with a cardioselective β_1 -blocker, such as bisoprolol, should be attempted under clinically controlled conditions in COPD patients with hypertension [19].

β -Blockers in COPD and CHF

β -Blockers need to be an integral part of therapy in most patients with CHF [12]. Extensive evidence supports the use of bisoprolol, carvedilol and metoprolol succinate in CHF. They are considered the cornerstone of management of CHF patients with impaired left-ventricular ejection fraction and have been shown to improve HF survival across the entire spectrum of disease severity. The place of β -blockers in the treatment of diastolic HF is still unclear [59]. The relative risk of mortality is lower in younger patients than in the older patients (aged >60 years) or in the very elderly (aged >75 years), and the effect is more evident for the non-selective β -blockers. Available evidence derives from several randomized, prospective clinical trials. It has been shown that a dose-related reduction in mortality is provided by a non-selective β -blocker such as carvedilol (–65%) and by several selective β_1 -blockers such as metoprolol, bisoprolol and nebivolol (approximately –35%), but not by bucindolol. However, the results of these studies could be generalized only to those patients whose characteristics are comparable to those who qualified to participate. It is worth mentioning that the vast majority of randomized clinical trial studying the clinical efficacy of different β -blockers in patients with CHF excluded COPD patients. When they were included, a selection bias is evident in most HF trials, since only approximately 10% of patients had COPD whereas the prevalence of COPD is higher in the general population with CHF. Since COPD patients have been frequently excluded from large trials and often treated with a suboptimal dosage, their efficacy in the management of both conditions is somewhat uncertain and still largely based on post hoc analyses of small subgroups.

Current guidelines recommend the use of β -blockers in CHF in the majority of patients with impaired left-ventricular ejection fraction [12], even if there is concomitant COPD, but evidence supporting their recommendation is of level C strength, i.e. based on expert opinion. Although β -blockers are recommended in all patients with systolic dysfunction, several surveys have shown their consistent under-utilization in COPD, as previously reported. The most cited reasons for non-adherence to clinical guidelines are the potential detrimental side effects of β -blockade on pulmonary function. In addition, these drugs tend to be administered at a lower-than-recommended dose.

Indeed, restrictive lung disease in patients with severe HF [60] and impaired alveolar gas exchange measured by diffusion for carbon monoxide (DLCO) has been described [61], regardless of COPD [62]. Recently, a double-blind, placebo-controlled study has shown that bisoprolol given at therapeutic doses for months in patients with stable HF and moderate-severe COPD significantly reduces FEV₁ and DLCO, but not residual volume [63]. However, changes in FEV₁ widely varied among patients, were likely to be within the range of long-term variability of this parameter and were of no clinical significance. On the other hand, response to bronchodilator treatment was preserved [63].

β -Blockers in COPD

The interaction of β -blockers with heterogeneous receptors localized in the human airways is not yet well understood. It is known that β -AR are implicated in the regulation of bronchomotor tone with 90% of them localized in the alveolar wall of the respiratory system; 70% of all β -AR are β_2 -AR, whereas β_1 -AR account for the remainder. β_2 -AR predominate in the bronchial smooth muscles, while β_1 -AR are 30% of β -AR present in the alveolar wall and 10% of β -AR in submucosal glands [21]. Their proportion changes depending on the organ and disease [25]. β_2 -AR present in presynaptic position on cholinergic nerves, and stimulation of these β_2 -presynaptic AR by β_2 -agonists inhibits the release of acetylcholine, a potent bronchoconstrictor [64].

β -Blockers may induce different pulmonary adverse effects that are relevant to COPD patients. The use of these drugs in COPD has been traditionally contraindicated, mainly for the report of acute bronchoconstriction after their administration [65]. The mechanism that mediates β -blockade-induced bronchoconstriction in

COPD patients is not entirely known. In patients with asthma, non-selective β -AR blockade may cause bronchoconstriction by antagonism of inhibitory presynaptic β_2 -AR on cholinergic nerves [66] that is associated with an increase in acetylcholine effects on M₂ cholinergic receptors. Of note, β -AR-induced bronchoconstriction does not occur in healthy subjects [67]. Moreover, the airways of healthy subjects are less sensitive to the constricting effect of acetylcholine. Patients with COPD showed an equal or better bronchodilation response to anticholinergic agents than to β_2 -agonists [68, 69], leading to the hypothesis that non-selective β -AR blockade causes bronchoconstriction by an unrestricted acetylcholine action [16]. In this case, the heterogeneity of M₂ cholinergic receptors in COPD patients may in part explain the variability in the airway response to β -AR blockade [70].

Alternatively, it could be that the bronchoconstrictor effect of β -blockers is not directly related to β -AR blockade [71, 72]. α_1 -AR blockade exerts a mild bronchodilator effect on COPD patients and abolishes propranolol-induced bronchoconstriction [73–75]; thus partial or complete β_2 -AR blockade with unopposed activation of α_1 -AR may be responsible for bronchoconstriction induced by non-selective β -blockers. The α_1 -AR-blocking activity of labetalol and carvedilol may be sufficient to offset β -AR blockade-induced bronchoconstriction in patients with COPD, but not in asthmatics [45, 76]. The difficulty to assess the exact mechanism of action of β -blockers has been stressed by the results of a recent study by Baker [26], who for the first time examined receptor affinity of a wide range of β -blockers using intact cells instead of membrane preparations, and the results are surprising. In fact, this study suggests that many ligands previously considered to have β_1 -selectivity, e.g. metoprolol, bisoprolol and atenolol, have a poor β_1/β_2 selectivity, whereas other β -blockers prescribed for cardiovascular disease, e.g. carvedilol, sotalol and timolol, have a higher β_2 selectivity. This finding could explain why the effects of metoprolol, a β_1 -selective blocker, on bronchial hyperresponsiveness are the same as those of propranolol, a non-selective β -blocker, in patients with COPD [77]. However, to our knowledge, effectiveness of the drugs in humans depends on more than just receptor affinity. In addition, the pharmacokinetic profile, absorption, metabolism, tissue distribution and elimination of the drug, as well as the longevity of action, are also important. Moreover, there are several different polymorphic variants of β -AR within the population and this may be associated with differences in drug affinity and action both in the clinical and laboratory setting.

Cumulative evidence from clinical trials and meta-analyses suggests that selective β_1 -blockers in patients with COPD have not significant adverse effects on FEV₁, respiratory symptoms or response to β_2 -agonists even in patients with advanced disease [78]. However, it should be noted that no long-term study was performed; most studies included few patients and not one study included patients with HF.

Bronchoconstriction may be the consequence of absence of cardioselectivity, since loss of cardioselectivity at high doses and unopposed stimulation of cholinergic muscarinic M₂ receptors and α -adrenoceptors can impede bronchodilation [16].

Indeed, at least in asthmatics bronchoconstriction induced by β -blockers is reversed by oxitropium bromide [79] and indoramin and phentolamine [73, 74]. Studies evaluating the effects of β - and α -blockers in COPD patients are scarce. At normal dosage, labetalol does not affect FEV₁ [80] in these patients. On the other hand, nebivolol, a third-generation β -blocker with highest β_1 -selectivity, results in good tolerability in patients with airway obstruction [81, 82]. Some degree of bronchoconstriction induced by β -blockers seems to be more frequent in COPD patients with partially reversible airflow obstruction [16, 61, 83]. However, a statistically significant reduction in FEV₁ has been found after a 4-month treatment with nebivolol, a β_1 -selective blocker, in moderate-severe COPD patients [63]. However, changes were within the range in most patients, and were not associated with changes in residual volume and increased clinical exacerbations [63]. It is remarkable to note that non-selective β -blockers decreased the bronchodilation response to inhaled β_2 -agonists [83], whereas nebivolol, a selective β_1 -blocker, did not [63].

A recent, controlled, crossover trial reported that the short-term administration of non-selective β -blockers increases bronchial hyperresponsiveness in irreversible COPD [77]. It is well known that bronchial hyperresponsiveness is associated with a tendency to a more rapid decline in FEV₁ in COPD patients and with increased mortality. However, the long-term effect of β -blockers was not examined; few patients were studied, some patients treated with placebo show an unexpectedly high bronchial hyperresponsiveness, suggesting selection bias, and mean changes in responsiveness – although significant – were within the range of variability [77]. However, the effect could be time dependent. Long-term administration of carvedilol and nadolol reduced airway hyperresponsiveness in a murine model of asthma; the mechanism of this phenomenon has been suggested to be asso-

ciated with the increase in β -AR density [42]. Recently, these data have been confirmed in humans: a small pilot study demonstrated that the administration of nadolol, which is currently contraindicated in asthmatic patients when chronically administered, shows a beneficial effect on most subjects with mild asthma [84]. The long-term effect of β -blockers should be more closely addressed.

Finally, β -blockers may influence gas exchange through a reduction in fluid re-absorption at the level of the alveolar surface [85–87].

Despite these adverse effects, in moderate-severe COPD patients, there is a large safety margin in β -blocker therapy that is not obvious for asthmatic patients [88]. Thus β_1 -selective blockers should not be routinely withheld from cardiac patients with coexistent moderate-severe COPD [61, 78].

It remains to be determined if systemic administration of non-selective β -blockers will have any effect on patients also taking short-acting and/or long-acting β_2 -agonists, the mainstay of COPD therapy. Whether chronic administration of β_2 -agonists increases the risk for hospitalization and mortality in patients with CHF is still debated [25]. Interestingly enough, a small pilot study indicated that salmeterol use was not associated with any exacerbation of HF [89]. However, it is clear that the issue of safety in long-term treatment with long-acting β_2 -agonists in COPD patients with concomitant CHF has not been solved yet. As previously discussed, chronic administration of β_2 -agonists leads to a 10-fold reduction in receptor affinity [84], thus reducing the binding of β_1 -blockers to β_2 -AR and favoring tolerance with the latter treatment [78]. On the other hand, it appears that chronic administration of β -blockers could increase β -AR density, therefore increasing the bronchodilator response of β_2 -agonists [37]. Indeed, controlled, prospective studies addressing the issue of concomitant, chronic use of different long-acting β_2 -agonists and different β_1 -blockers in COPD patients with CVD are lacking.

Principles of β -Blocker Treatment in COPD

The decision to begin β -blocker therapy should be considered on a 'case-by-case basis' in COPD patients and should be left to a specialist. Clinical and perhaps genetic factors should be considered. There is increasing evidence that genetic variation in the β_1 -AR locus affects the impact of β -blockers. It is of interest that the β_1 -Arg389Gly polymorphism consistently appears to predict the efficacy of β -blockers [27].

Close definition of respiratory disease(s), i.e. COPD or COPD plus asthma, is required. Indeed a consistent proportion of patients with respiratory symptoms has been diagnosed with COPD without clear clinical and objective functional evidence. In addition, at least in primary care, the majority of patients with COPD have only mild-moderate airflow obstruction, facilitating cardioselective β_1 -blocker treatment without an increased risk of unwanted pulmonary effects. Indeed, it is worth mentioning that β -blockers have never been studied in patients with very severe COPD ($FEV_1 < 30\%$ of predicted or $FEV_1 < 50\%$ plus chronic respiratory failure) [39].

Cardioselective β_1 -blockers (or non-cardioselective β_1 -blockers with α -blocking activity) should be selected [35, 36]. Cardioselective β_1 -blockers with ISA should be avoided since they might reduce response to β_2 -agonists by downregulating β_2 -AR [25]. Complete knowledge of the pharmacological properties of each molecule is advisable [35, 36]. Potential age- and possibly gender-related changes in β -blocker pharmacokinetics should be considered [38]. In addition, a certain degree of variability in the individual response to β -blockers might be linked to pharmacogenetics [90].

Only β -blockers tested in clinical trials (namely carvedilol, long-acting metoprolol and bisoprolol) should be used in asymptomatic or symptomatic LV systolic dysfunction, because their survival benefit has been proven. The cardioselective β_1 -blockers metoprolol and bisoprolol have been reported as the first choice for the prevention and treatment of CAD [91].

Thus cardioselective β_1 -blockers (without ISA and with a short half-life) should be administered at the lowest dose (such as bisoprolol 1.25 mg daily or nebivolol 1.25 mg daily) in mild-moderate COPD for a minimum period of 1 month before gradual and careful upward titration of the dose to the target range causing a significant β -blockade over several (8–12) weeks to ensure safety ('start low and go slow') [12]. For instance, the following regime has been proposed for bisoprolol: starting dose 1.25 mg once daily, which is successively increased to 2.5, 5.0, 7.5 and 10 mg every 2–4 weeks, according to tolerance [63]. It should be emphasized that such a progressive and individualized method of administration was critical for the transformation of β -blockers from contraindicated agents in CHF to a critical component of standard management. Moreover, there is a tendency in clinical practice and in non-specialized settings to administer a daily dose which is lower than that in randomized, controlled trials, likely as a consequence of the reluctance of physicians to prescribe the recommended dose. ' β_1 -Selective'

agents, e.g. bisoprolol, celiprolol and metoprolol, lose selectivity at high doses, becoming effectively non-selective.

Early mild deterioration of pulmonary symptoms after initiation of a β -blocker may not warrant its prompt discontinuation. Moreover, while titrating the dose, it would be advisable to pretreat patients with an anticholinergic agent such as tiotropium and to use ipratropium or oxitropium bromide for on-demand rescue treatment.

Since even selective β_1 -blockers may have different pulmonary effects, their use in at-risk COPD patients should be always guided by the combination of lung function evaluation (FEV_1 for airflow obstruction and residual volume for hyperinflation) and assessment of DLCO. The latter measurement is recommended when HF comorbidity is present [92, 93].

Prediction of a detrimental effect of β -blockers on lung function in COPD patients has been based on the presence of a significant acute bronchodilator response to β_2 -adrenergic agonists and anticholinergic agents [19] and/or on the presence of methacholine responsiveness [94]. Neither method is however satisfactory. Indeed, under carefully controlled conditions up to 50% of COPD patients demonstrate a significant response to bronchodilators [95], thus limiting the utility of this method. Most but not all guidelines for CVD suggest that the presence of reversibility of obstruction should be measured in COPD patients before introducing β -blockers. However, a large European trial performed in the primary-care setting showed that few patients performed baseline pulmonary function tests despite the fact that most patients were on bronchodilator treatment [33]. In addition, the presence of methacholine responsiveness in COPD has been regarded as an index of the presence of 'an asthmatic component'. These patients should be at risk of a greater bronchoconstrictive response to β -blockers. However, a large proportion of COPD patients (up to 70%) may also show bronchial hyperresponsiveness [96]. Alternatively, methacholine responsiveness has been measured during short-term treatment with β -blockers [77]. Indeed, methacholine response increased more following the administration of non-selective β -blockers. The long-term effect has never been studied, but at variance it could be beneficial [42, 83]. However, such a method cannot be used in patients with moderate-severe obstruction [97] and is highly influenced by the degree of airflow obstruction. It remains a research tool rather than a clinical practice protocol. Perhaps genotype testing for β_2 -AR would prove to be useful in the future to detect patients at risk of developing a more severe bronchoconstrictive response.

Additional factors should be considered in case of sub-optimal results. There is widespread recognition of patient-to-patient variability in drug response. Pharmacogenetic studies will help to determine the response of individual patients to β -blockers [90]. Up to now, physicians cannot anticipate who of their patients will benefit most or at all. Consistent systemic inflammation associated with COPD may accelerate the metabolism of β -blockers, leading to reduced efficacy. Evidence indicates that females may demonstrate a greater response to β -blockers. However, data in female patients are very limited and results from males may not be simply extrapolated to females. Much uncertainty exists regarding the tolerability and relative efficacy of β -blockers regardless of age. Thus doubts remain about their advisability in the elderly. However, the blood pressure-lowering effect of β -blockers is more marked in the elderly than in younger patients, and thus they may require a lower dose.

Conclusion

At present, data on the safety of selective β_1 -blockers in patients with COPD were derived from studies that generally included small groups of poorly characterized patients with treatments given for a short period of time. Indeed, there are still several questions that need to be addressed. However, the well-proven efficacy of β -blockers on survival in several high-risk CVD patients, including CHF, should prompt their use in the large proportion of COPD patients who had such co-morbidities. Since absolute contraindications are difficult to predict apart from overt history of bronchial asthma, it is not logical to abandon the use of selective β_1 -blockers in the presence of a diagnosis of COPD [12, 83] or possibly in the presence of severe disease, too [12]. β_1 -Blockers should be carefully selected not only on the basis of cardioselectivity and proven efficacy on mortality, but also with respect to the challenging deleterious effects on respiratory symptoms, lung function and gas exchange in individual patients. In addition, the dosage of selective β_1 -blockers should be progressively titrated on a case-by-case basis with regular monitoring over a period of several weeks since observational studies suggest that the mean daily dose could be half of the target dose recommended in randomized controlled studies.

Although the benefits of chronic treatment with selective β_1 -blockers may far outweigh the risks of induced bronchoconstriction [12], the use of β -blockers is seriously inadequate since the diagnosis of COPD per se is

still a barrier or is perceived as a serious contraindication by many physicians, particularly in case of potential pulmonary sequelae. Thus their erratic use is a direct consequence of reluctance and prejudice [34]. It has been estimated that the reluctance to use β -blockers in patients with CHF according to current guidelines contributes to approximately 7,800 deaths per year in the UK, a significant proportion of them being patients with both CHF and COPD [98]. Both primary- and secondary-care physicians need greater support in managing COPD patients requiring selective β_1 -blockers. Ultimately only changing the prejudice will solve the dilemma of the optimal use of β -blockers in COPD.

As pneumologists we can no longer tolerate that only 30% patients with COPD and CHF have confirmatory spirometry and echocardiography to substantiate the diagnosis, while in 50% of them only echocardiogram was performed [99]. As physicians, we can no longer tolerate that >50% of patients with HF without COPD are treated with β -blockers compared to only 20% of patients with HF and COPD [11, 100], and that on average the daily dosage of β -blockers remains far below the target doses [100], strongly suggesting that clinicians often fail to perform a substantial dose-ranging study, and that β -blockers for which no substantial trial in HF exists are prescribed in 10–20% of patients with HF and systolic dysfunction [98, 100].

The importance of including β -blockers, a pivotal treatment modifying and prolonging life, in the standard treatment of most COPD patients with coexisting CVD should be supported by a detailed, critical analysis of the large body of scientific evidence that demonstrates the life-saving efficacy and safety of the long-term treatment with β -blockers. Additionally, we should call for results of long-term, prospective, clinical trials fully addressing the impact of this fundamental treatment in patients with COPD complicated by CVD in the real world. Meanwhile, pneumologists and cardiologists should develop a detailed and standardized protocol for individual COPD patients based on current knowledge and on wide testing of pulmonary function to guide and enhance the safe use of selective β_1 -blockers in everyday practice, which could significantly reduce the physicians' mistrust of β -blockers in COPD patients. Hopefully, we are at the beginning of a new era in which the use of β -blockers would be characterized by a detailed clinical evaluation, pathophysiological measurements, and knowledge of the pharmacological properties of each molecule and its pharmacokinetic and pharmacodynamic parameters in different populations, and efficacy being predicted by pharmacogenomics.

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