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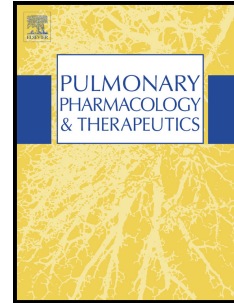
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Pharmacological modulation of β -adrenoceptor function in patients with coexisting chronic obstructive pulmonary disease and chronic heart failure

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Summary

Pharmacological modulation of β -adrenoceptor function is one of the critical issues in the treatment of patients with concurrent chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF). A volume of published evidence sustains the role of long-acting β_2 -agonists in the treatment of stable COPD, but β -agonists seem to be detrimental when used for long term in CHF. β_2 -agonists may exacerbate heart failure and, in any case, they induce adverse cardiac effects in COPD patients with pre-existing cardiovascular disease. The adverse effects of β_2 -agonists are likely to be exacerbated in COPD patients with coexistent CHF. β -Blockers are the standard treatment in CHF, but they can worsen FEV₁ and airway hyperresponsiveness and reluctance exists to prescribe these agents to COPD patients, despite the anticipated beneficial cardiovascular effects. Although the literature is reassuring, there are currently no prospective long-term studies on the safety of β -blockers in COPD. Therefore, although β -blockers can be introduced in any medical setting for treating patients with concurrent COPD and CHF, it still seems appropriate to only use those β -blockers that are more selective for the β_1 -AR but without ISA at the lowest dose and to titrate them slowly with attention to lung function and symptoms, adding an inhaled antimuscarinic agent when bronchodilation is needed.

Introduction

The prevalence of chronic heart failure (CHF) in patients with chronic obstructive pulmonary disease (COPD) is known to range from 20% to 32% [1-7]. This high prevalence of CHF in patients with COPD is not surprising, because COPD and CHF share smoking as a common risk factor, and, moreover, it is likely that low-grade systemic inflammation accelerates progression of coronary atherosclerosis, which ultimately results in ischemic cardiomyopathy [8].

Although the coexistence of COPD and CHF is common, it is often unrecognized because dyspnea and functional intolerance are common presenting symptoms and this makes the coexistence of both conditions difficult to diagnose regardless of patients age [9]. Moreover, patients with coexisting COPD and CHF may have therapeutic constraints that have not been comprehensively investigated. Pharmacological modulation of β -adrenoceptor (β -AR) function is one of the critical issues in the treatment of these patients [10].

Interfering with β -AR function is central in the treatment of both COPD and CHF. In fact, inhaled β_2 -agonists are one of the mainstays of COPD therapy [11], whereas β -antagonists, also called β -blockers, reduce mortality and morbidity in patients with CHF [12]. Consequently, pharmacological modulation of β -AR function is recommended by current COPD [11] and CHF guidelines [12], respectively.

Traditionally, the treatment of COPD is based on the use of long-acting bronchodilators, mainly long-acting β_2 -agonists (LABAs) and/or long-acting antimuscarinic agents, as well as the use of short-acting β -agonists (SABAs) as rescue medication, but it has been suggested that the use of β_2 -agonists might lead to an increased risk for adverse events in patients suffering from COPD [13] as well as in those suffering from CHF [10, 14]. On the other hand, despite clear evidence of the effectiveness of β -blockers in the management of patients with CHF, the use of these agents has traditionally been contraindicated in COPD, mainly because of anecdotal evidence and case

reports citing acute bronchospasm [15] and increased airway hyperresponsiveness (AHR) [16] after their administration.

The objective of this review is to verify whether the evidence supports or refutes the pharmacological modulation of β -AR function in patients with coexisting COPD and CHF.

β -ARs in human airways and heart

β -ARs are subdivided into three types; β_1 , β_2 and β_3 . They are members of the seven-transmembrane spanning family of G-protein-coupled receptors related to bacteriorhodopsin. There is a 65% to 70% homology between β_1 - β_3 and β_2 -ARs.

β -ARs and human airways

β_2 -ARs are widely distributed in human airway smooth muscle [17]. Radioligand binding studies on lobectomy specimens have shown β_2 -AR density to increase with increasing airway generation, with high levels in the alveolar region [18]. β_2 -ARs are also expressed on many pro-inflammatory and immune cells, including mast cells, macrophages, neutrophils, lymphocytes, eosinophils, epithelial and endothelial cells, and both type I and type II alveolar cells. β_2 -AR stimulation produces airway relaxation, but prolonged β_2 -AR activation leads to a decrease in receptor responsiveness (*i.e.* desensitization) that differs depending on the cell type [19]. The rate at which a β -agonist drives receptor desensitisation parallels its intrinsic efficacy [10]. Intrinsic efficacy refers to the ability of a drug, independent of tissue conditions, to interact with a receptor to activate its downstream signal transduction pathway. The intrinsic efficacies of commonly used β -agonists are listed in table 1.

Also β_1 -ARs are present in the lungs. They account for 10% and 30% of the ARs on submucosal glands and alveolar walls, respectively [17].

β -ARs and the heart

Although β_1 -ARs are classically described as the key participants in triggering and regulating cardiac contractility, stimulation of both β_1 -ARs and β_2 -ARs leads to positive inotropy via coupling to adenylyl cyclase and generation of cAMP [20]. Bristow et al. [20] demonstrated that the proportions of β_1 -AR and β_2 -AR in normal hearts are 77 and 23%, respectively. Functional β_1 -ARs and β_2 -ARs coexist on atria and ventricles with β_1/β_2 -AR ratio of about 60 to 70%/40 to 30% in the atria and about 70 to 80%/30 to 20% in the ventricles [21]. Interestingly, Rodefeld et al. [22] showed that in human sinoatrial nodes, total β -AR density is about 3-fold higher than that in the adjacent atrial myocardium; although the β_1 -AR subtype predominates in both regions, the β_2 -AR density is about 2.5-fold higher in the sinoatrial node than in the right atrial myocardium and this is consistent with physiologic studies that implicate this receptor in regulating cardiac chronotropism. β_2 -ARs are also present on adrenergic nerve terminals in the heart, where they facilitate noradrenaline release [23].

The functional responses mediated by β_1 -ARs and β_2 -ARs are not necessarily different, likely because human cardiac β_2 -ARs are more effectively coupled to adenylyl cyclase than are β_1 -ARs [24]. There is solid documentation of directly β -AR-mediated positive inotropic and chronotropic effects in humans *in vivo* using β_2 -agonists such as terbutaline or salbutamol. These effects are slightly antagonized by β -blockers that are more selective for the β_1 -AR such as bisoprolol or atenolol [24]. The activation of prejunctional β_2 -ARs might contribute to the cardiac effects of β -agonists because it leads to enhanced noradrenaline release, at least at high doses [24].

β -AR stimulation provides the most powerful mechanism to augment cardiac contractility in response to a 'fight-or-flight' situation, but prolonged exposure of β -ARs to an agonist causes desensitization [25].

Reasons for modulating β -AR function in patients with COPD and chronic heart failure

The presence of β -ARs in human airways and heart explains why the modulation of β -AR function is important in influencing pulmonary and cardiac functions. In COPD patients, β_2 -agonists interact with the β_2 -ARs and relax airway smooth muscle. On the other side, overwhelming evidence supports a major role for the β -AR system in heart failure. While this system is ideally suited for short-term increases in cardiac performance, its long-term activation is apparently detrimental. These damaging effects appear to be mainly due to stimulation of the β_1 -AR subtype, but the responsible signalling pathways need to be identified.

In the failing heart, the respective proportions of β_1 -ARs and β_2 -ARs are 60 and 38% [21]. This decrease in the proportion of β_1 -ARs and the relative increase in the proportion of β_2 -ARs have been postulated to be a result of selective down-regulation of the β_1 -ARs, with little or no change in β_2 -ARs [21]. It is a protective mechanism that counteracts deleterious effects induced by chronic sympathetic activation [21]. Consequently, the failing heart becomes more dependent on the β_2 -ARs for inotropic support. However, the activation of these receptors may also alter the cardiac electrical stability, increasing the propensity for the formation of malignant arrhythmias in the diseased heart.

β_2 -agonists

COPD

A volume of published evidence supports the role of LABAs in the treatment of stable COPD. They induce prolonged bronchodilation and translate this action into other health-outcome measures related to quality of life, such as the severity of dyspnoea, exercise capacity, and, mainly, number and severity of exacerbations [26].

A meta-analysis of 9 randomized clinical trials that lasted at least one year, with > 3,500 patients, found that when salmeterol was used instead of placebo or usual therapy, patients were less likely to withdraw early and suffer an exacerbation, and had a better health status and a greater increase in FEV₁ [27]. There was no tachyphylaxis or death reported although some papers

indicated that duration of action over time and peak effect of LABAs might be subject to tachyphylaxis [28, 29]. Also a further meta-analysis supported the beneficial effects of the use of LABAs in patients with stable moderate and severe COPD, with significant benefits in airflow limitation measures, health-related quality of life, and use of rescue medication with SABAs [26]. The meta-analysis did not document an increased risk for respiratory deaths [30].

On the contrary, in the meta-analysis of Salpeter et al. [31] β_2 -agonists resulted in an increased rate of deaths, possibly owing to a reduction in disease control. Moreover, some patients with COPD are at risk of cardiovascular mortality because inhaled β_2 -agonists may precipitate cardiovascular events in susceptible patients [10, 13, 14]. In fact, numerous substrates for ventricular arrhythmia exist in these patients: hypoxia, acidosis, hypercapnia, sympathetic activation, tachycardia, hypokalaemia, and QTc prolongation secondary to inhaled β_2 -agonists [10, 13]. However, the TORCH (TOwards a Revolution in COPD Health) study [32], in which more than 6,000 patients with COPD were randomized to salmeterol, fluticasone, combination salmeterol-fluticasone, or placebo, documented that the overall mortality, cardiovascular mortality, and cardiovascular-related adverse events were no greater in the salmeterol group compared with any of the other groups.

Chronic heart failure

It remains unknown whether the use of β_2 -agonists leads to an increased risk of heart failure and/or it may affect the risk of hospitalization among patients with existing CHF. β_2 -agonists are efficacious in improving cardiac performance in patients with CHF because they enhance cardiac and stroke volume indexes in a dose-dependent manner [33-35]. For these reasons, β_2 -agonists are often used for the short-term enhancement of heart contractility and support of the circulation.

Nonetheless, data from the Acute Decompensated Heart Failure National Registry Emergency Module (ADHERE-EM) [36] demonstrated that 14% of patients who present with dyspnoea are treated for COPD when COPD is absent and acute decompensated heart failure is the cause of dyspnoea.

Inhaled β_2 -agonist use in these heart failure patients without COPD appeared to be associated with worse outcome. Au et al. [14] identified an increased risk of heart failure hospitalization among patients with left ventricular (LV) systolic dysfunction who received a β_2 -agonist within 3 months of the hospitalization. This risk increased as the number of canisters used per month increased; the effect persisted after adjustment for other pulmonary therapies, including ipratropium and steroids. The mortality risk was also higher for patients treated with a β_2 -agonist, but the effect was only significant in patients who received greater than or equal to 3 bronchodilator canisters per month.

There is evidence that β -agonists, while useful acutely, lead to increases in mortality with long-term use [37]. Although β -agonists can relieve symptoms and improve hemodynamic parameters, their chronic administration has been associated with increased mortality in all sufficiently powered clinical trials with a variety of drugs ranging from strong to weak agonists. Actually, some reports suggest the presence of an association between β_2 -agonists and the risk of incident CHF [38, 39]. The Washington, DC, Dilated Cardiomyopathy Study compared 129 newly diagnosed cases of idiopathic dilated cardiomyopathy to 258 randomly dialed neighbourhood controls [38]. An association between idiopathic dilated cardiomyopathy and history of emphysema or chronic bronchitis (OR, 4.4), asthma (OR, 1.9), oral β -agonists (OR, 3.4), and β_2 -agonist inhalers or nebulization (OR, 3.2) was demonstrated. A total of 20% of the cases had a reported history of β_2 -agonist inhaler use compared with 6.7% of the controls.

On the contrary, the Ambulatory Care Quality Improvement Project (ACQUIP) [39] found no association between the use of inhaled β_2 -agonists and the risk of heart failure (1-2 canisters per month, OR, 1.3; ≥ 3 canisters per month, OR, 1.1). However, among the cohort with a history of CHF, there was a dose-response association between the number of inhaled β_2 -agonists and the risk of hospitalization for CHF (1-2 canisters per month, adjusted OR, 1.8; ≥ 3 canisters per month, adjusted OR, 2.1). The increase in risk among patients with existing CHF was independent of history of COPD, steroid use, β -blocker use, ACE inhibitor use, myocardial ischemia, and cardiovascular risk factors.

This is an important finding because many patients with underlying cardiovascular diseases such as CHF have concomitant obstructive airway disease [40].

Whatever the case may be, the observation that β_2 -agonists may exacerbate heart failure is supported by physiologic observations. β_1 -ARs are down-regulated and desensitized among patients with LV systolic dysfunction and β_2 -ARs, although desensitized, are found in normal numbers and represent a higher proportion of total β -ARs [41, 42]. Among patients with heart failure, β_2 -agonists augment cardiac function but, with regular exposure to β_2 -agonists, myocardial β_2 -ARs become desensitized and down-regulated. [43, 44]. Moreover, chronic β_2 -ARs stimulation elevates G_i expression [45]. The coupling of β_2 -ARs to G_i proteins negatively regulates the G_s -mediated contractile response in the heart of many mammalian species [45]. Intriguingly, the Ile¹⁶⁴ polymorphism of the β_2 -AR, which leads to a dysfunctional receptor, has been demonstrated to be associated with decreased exercise tolerance and a 5-fold increase risk of death among patients with CHF [46]. The possibility that chronic β -AR stimulation induces myocardial, but not systemic, elaboration of TNF- α , IL-1 β , and IL-6 [47] is another important finding. In fact, evidence suggests that proinflammatory cytokines are capable of modulating cardiovascular function by a variety of mechanisms, including promotion of LV remodelling [48], induction of contractile dysfunction [49], and uncoupling of myocardial β_2 -ARs [50].

Although the possibility that β_2 -agonists might exacerbate heart failure, Ng et al. [51] explored if chronic inhaled salmeterol therapy, 100 μ g bid, improved pulmonary function without augmentation of neurohormonal systems or ventricular ectopy in symptomatic heart failure subjects with LV ejection fraction <40%. Salmeterol significantly increased mean rate-pressure product by 5%, and FEV₁ without producing measurable effects on neuroactivation or ventricular ectopy. The safe profile of salmeterol was also confirmed by the Drug and Safety Research Unit and the School of Medicine at Southampton (UK) [52]. Using the prescription-event monitoring technique, researchers from this Unit re-examined the safety issue for salmeterol, and bambuterol, a

long-acting oral agent and prodrug of terbutaline. There was an excess of non-fatal “cardiac failure” in the bambuterol group during the first month, and a lower but increased incidence during the second to sixth months, whereas there was no excess in the salmeterol group. This finding raised the question why bambuterol and not salmeterol caused CHF. It is likely that this was linked to the route of administration (oral instead that inhaled) and the different dose, significantly higher with bambuterol that induced a high systemic bioavailability and, consequently, higher risk of side effects.

β -AR blocking drugs

Chronic heart failure

When β -blocking drugs are used for coronary artery disease or hypertension, they acutely produce a decrease in contractility in patients with heart failure. Also, patients with recently decompensated heart failure are very susceptible to worsening even with low doses of this class of drugs. The initiation of β -blockade in these patients might be expected to cause worsening heart failure by interfering with the positive inotropic and lusitropic actions of endogenous catecholamines [53]. Consequently, the use of β -blocker therapy was once thought to be contraindicated in patients with heart failure with systolic dysfunction.

Paradoxically, the chronic use of certain β -blockers has been the treatment that has had the most success for decreasing mortality in CHF. Since the pioneering work in the 1970s [54], it took two decades until β -blockers turned from contraindication to standard treatment in heart failure [55] (table 2). Blocking β -ARs when cardiac function depends on sympathoadrenergic drive long appeared counterintuitive. Today, studies with bisoprolol, metoprolol, and carvedilol (Cardiac Insufficiency Bisoprolol Study (CIBIS II) [56], Metoprolol CR/XL Randomised Interventional Trial in Congestive Heart Failure (MERIT-HF) [57] and Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) [58], respectively,) show a similar reduction in the risk of death by a third or more in patients with CHF who were already receiving ACE inhibitors and diuretics, a benefit greater than of any other drug used in heart

failure. Metoprolol and bisoprolol are 75-fold and 120-fold more selective for β_1 -ARs compared with β_2 -ARs in humans, respectively [59], and have modest inverse activity (i.e., they decrease the spontaneous activity of the receptor in the absence of agonist) [60], whereas carvedilol is nonselective, shows no inverse activity [60], dissociates slowly from the receptor [61], and is a radical scavenger and α_1 -antagonist.

All three compounds led to similar clinical results, but carvedilol was superior to metoprolol in the COMET trial [62]. Methodological criticism aside, this trial does not answer the questions of possibly protective β_2 -ARs and whether the additional properties of carvedilol are important. A role for intrinsic sympathomimetic activity (ISA), an ancillary pharmacologic property of some β -blockers, is supported by the observations that the strong partial agonist xamoterol was detrimental in heart failure [63], and the weak partial agonist bucindolol [64] was ineffective in the BEST trial [65]. The beneficial β -blockers are neutral (carvedilol) or inverse agonistic (bisoprolol, metoprolol) [60]. However, because of the low constitutive activity of the β_1 -AR, it is uncertain how important inverse agonism is. Taken together, the question is still open which pharmacological properties of β -blockers make them effective in CHF (table 3).

So far there is not a conclusive explanation that is able to simultaneously support a short-term detrimental effect with a chronic beneficial effect. However, the fact that the beneficial effect of the antagonist is not observed for weeks or even months after equilibrium of β -blockade is achieved suggests this is a compensatory mechanism, indirectly caused by the β -AR blockade and not due to the β -blockade per se [66].

COPD

β -blockers are known to worsen FEV₁ and AHR in asthma, and therefore reluctance exists to prescribe these agents to COPD patients as well, despite the anticipated beneficial cardiovascular effects (table 4). Most of the adverse pulmonary effects exerted by β -blockers in COPD patients are related to interference with β_2 -AR-mediated bronchodilation. Various studies have

identified relevant differences in the impact on airway function, depending on whether a β -blocker is β_1 -AR selective or β_1 -AR nonselective [67-72]. β_1 -blockade does not attenuate β_2 -agonist induced bronchodilation. However, also β_1 -blockers can adversely affect airways. In fact, all β -blockers that apparently are more selective for the β_1 -AR block β_2 -ARs when their concentrations are high enough [73]. Moreover, the so-called β_1 -blockers are not completely β_1 -selective, which could mean that they might have some affinity for β_2 -ARs on airway smooth muscle [74]. This means that with large doses of all β -blockers β_1 -AR selectivity is lost and all β -ARs are at risk for being blocked. Therefore, the classification into 'cardioselective' β_1 -blockers and nonselective β -blockers is important, but oversimplified.

The therapeutic importance of ISA in COPD patients is questionable. Apparently, ISA seems to be at least as important as β_1 -selectivity in reducing the increase in airway resistance that results from β -blockade both at rest and during exertion [75]. Moreover, it reduces the bronchoconstrictor response to inhaled histamine during β -blockade in asthma patients [76]. Decalmer et al. [77] examined the effects of approximately equipotent single oral doses of β_1 -antagonists (atenolol, 100 mg; metoprolol, 100 and 300 mg) and four nonselective β - ($\beta_1 + \beta_2$) blockers (propranolol, 100 mg; oxprenolol, 100 mg; timolol, 10 mg; and pindolol, 5 mg) on FEV₁ in 10 asthmatic patients. Pindolol is the only agent with ISA. All drugs caused a fall in FEV₁, but only atenolol did not differ significantly from placebo in this respect. Moreover, the four nonselective β -blockers inhibited the bronchodilator response to inhaled isoprenaline, whereas the selective β_1 -blockers allowed some bronchodilation. These observations indicate that pindolol is potentially dangerous at least in asthmatic patients. There is also evidence that treatment with β -blockers that have ISA is associated with down-regulation of β_2 -AR [78]. This finding is consistent with data showing that β -antagonists with ISA did not produce the increase in β_2 -agonist response that was seen with β -antagonists without ISA [79-81]. Since agents with ISA offer less cardioprotection than do β -antagonists without this ancillary property, the use of these drugs should be severely restricted.

In any case, the cumulative evidence from trials and meta-analyses indicates that 'cardioselective' β_1 -blockers should not be routinely withheld from patients with COPD because the benefits of β_1 -blockers in patients with COPD who also have cardiac disease far outweigh the risks [82]. Systematic Cochrane Database Reviews and further meta-analyses by Salpeter et al. of RCTs of patients with reversible airway disease and COPD exposed to single dose or continued treatment with what they called 'cardioselective' β -antagonists have been published [83-86]. Although they found that acute (single dose) β -blockade resulted in a small reduction in FEV₁, this was mitigated by a modest increase in FEV₁ with β_2 -agonists. Moreover, chronic treatment (3-28 days) produced no change in FEV₁, symptoms, or inhaler use, whilst inducing a modest response to β_2 -agonists. In addition, no consistent exacerbation of airways disease was recorded in the 80 trials identified. Recently, van Gestel et al. [87] reinforced this view by providing solid proof that, in carefully selected patients with COPD undergoing vascular surgery, β_1 -blockers are safe and beneficial in prolonging survival.

Discussion

Regarding the utilization of β -agonists, there is no solid proof at present time that supports or denies their use in the treatment of CHF, although some evidence indicates that therapy with inhaled β -agonists is associated with an increased risk for CHF decompensation and all-cause mortality in patients with CHF [38, 39]. In effect, CHF has a tremendously high mortality and morbidity. Therefore, it is not surprising that any adverse effect of a drug on survival would be much easier to observe and document in this disease [88]. It must be mentioned that inhaled β_2 -agonists induce adverse cardiac effects in COPD patients with pre-existing cardiovascular disease [89]. In particular, the adverse effects of β_2 -agonists are likely to be exacerbated in COPD patients with coexistent CHF [90].

Regarding the utilization of β -blockers, the information from trials and meta-analyses of patients with COPD exposed to continued treatment with those β -blockers that are more selective for the β_1 -AR is reassuring, but there are two

fundamental concerns. First of all, the long-term safety of β_1 -blockers in airways disease has not been proven. In general, the studies were limited to few weeks, excluded patients who had recent exacerbations and were deemed to be at higher-risk, included younger patients, and may have been subject to publication bias [91]. The second concern is linked to the fact that recent analyses that examined the affinity of a wide range of so called β_1 -blockers to a homogenous population of human β -AR subtypes expressed in cell lines, showed a more limited preference for β_1 -AR than previously thought, suggesting that many β_1 -blockers block β_2 -ARs in bronchi in addition to blocking β_1 -ARs in the heart [90]. This finding could explain why the effects of the β_1 -blocker metoprolol on AHR are the same as those of the nonselective β -blocker propranolol in patients with COPD [16].

Therefore, the advice is that prescribing β -blockers for COPD patients should be restricted to specialists who are able to monitor patients closely. In reality, many general practitioners (GPs) may feel reticent about providing repeat prescriptions to COPD patients started on β -blockers by cardiology specialists. A commonsense approach would be only to prescribe these drugs when the GP knows the patient is stabilised on them, when they are shown to be beneficial to the patient, and when the consultant and GP agree on required monitoring and follow-up, and the responsibility for it [92].

This issue needs careful consideration. Traditionally, the treatment of COPD is based on the use of long-acting bronchodilators although the potential risk for adverse cardiovascular events in patients with COPD that is present even when inhaled anticholinergic are used [10, 93]. β -Blockers might neutralize the actions of β -agonists, so that the risk of adverse cardiovascular events associated with these agents might be different in subjects already using β -blockers than among nonusers of β -blockers. However, there is evidence that β -blockers lead to an increase in the density of β -ARs [94]. This effect might suggest an bigger risk associated with the concomitant use of β -agonists and β -blockers in COPD. Apparently, β_1 -blockers are associated with an augmented bronchodilator response to β -agonists [91]. This is a clear indication of facilitated β -AR stimulation, but facilitated β -AR stimulation would also

increase heart rate and myocardial oxygen demand [10]. Case-control studies demonstrated an association between β_2 -agonist use and an increased risk for myocardial infarction, CHF, cardiac arrest, and acute cardiac death. Intriguingly, the absence of a concurrent possible protective effect of β -blockers has been suggested in this situation [95] but, unfortunately, the efficacy of concomitant β -blockers to offset the adverse cardiovascular effects of β_2 -agonists in COPD patients with coexistent CHF has not yet been assessed in clinical trials.

If the above considerations lead to fear of the unconditional use of β -blockers in COPD, one should also consider a pharmacologic phenomenon that is opposite of what we have just described. In effect, exposure to β -agonists may alter β -ARs such that the affinity for ligands is reduced 10-fold [96]. Consequently, prior exposure to β -agonists may reduce binding of antagonists to β_2 -ARs. This relationship may explain the suggested high tolerance for β -blockers in patients with COPD, who routinely inhale β_2 -agonists [83-86].

The lack of certainties about how to treat a patient with concurrent COPD and CHF leaves us still doubt about what to do, even for the obvious ethical, but also legal (malpractice), implications of our choices. Unfortunately, there are currently no prospective long-term studies on the safety of β -blockers in COPD and, moreover, the beneficial effect of β -AR blockade in patients with coexistent CHF and COPD is difficult to ascertain because such patients have been excluded from all large efficacy trials to date. Nonetheless, the literature is reassuring, although a retrospective analysis assessed the use of β -blockers in CHF patients with COPD showed that the long-term use of β -blockers did not increase the risk of respiratory complications and there was no difference in outcomes with the use of so called 'cardioselective' or nonselective β -blockers and the conclusion was that 'cardioselective' β -blockers without ISA are preferred until future studies resolve this issue [97]. In the recent publication of the Heart Failure Society of America on heart failure practice guidelines [98], β -blocker therapy is recommended in the great majority of patients with LV systolic dysfunction, even in the presence of concomitant COPD. They recommend that β -blockers are initiated at a low dose and uptitrated gradually

in two weeks intervals. The guidelines also recommend that patients with difficulties in initiating, uptitrating, or maintaining β -blocker therapy to be referred to a physician with expertise in the management of these patients. This is to ensure that no patient is denied the benefits of β -blockers. Therefore, although β -blockers can be introduced in any medical setting for treating patients with concurrent COPD and CHF, we believe that it still seems appropriate to only use those β -blockers that are more selective for the β_1 -AR but without ISA, at the lowest dose and to titrate them slowly (table 5) with attention to lung function and symptoms, adding an inhaled antimuscarinic agent when bronchodilation is needed [15, 99].

β -Blockers with β_2 -agonist activity (celiprolol) might preferable to conventional β_1 -blockers, but there is some risk that bronchospasm may occur in certain individuals and the bronchodilator response to inhaled β_2 -agonists might be impaired [15]. β_1 -blockers that modulate the endogenous production of nitric oxide (nebivolol) are another interesting option. Nebivolol seems to be more useful than other β -blockers in African American patients and those suspected of having decreased nitric oxide bioavailability as an underlying pathophysiology of disease [100], and, moreover, in seniors with heart failure [101]. Nonetheless, more research is needed to better assess the impact of these drugs on patients with COPD [102].

Elderly is a particular issue in clinical practice since the prevalence of both CHF and COPD increases with age [103, 104]. Human aging is associated with an increase in the activity of the sympathetic nervous system [105, 106] and a diminished β -AR response to catecholamine [107, 108]. As a consequence, an alteration of bronchodilator response to β -agonists in elderly people has been suggested [109], and also treatment with β -blockers can be more challenging due to desensitization of β -ARs and variable pharmacokinetic responses that occur with age (potentially decreased absorption, metabolism and excretion) [110]. It is clear that it is imperative to individualize therapy for each patient [111] but the implementation of a safe and effective treatment may be more difficult in elderly. Senescence, concurrent diseases, malnutrition, polipharmacy may influence presentation and clinical course of CHF and COPD

and interfere with their management. For this reason, a careful monitoring of treatment is recommended when dealing with this population.

Finally, it must be mentioned that β_1 - and β_2 -AR responses to drug treatment exhibit marked interindividual variability [112-114]. At present, it seems to be clear that β -AR polymorphisms do not play a role as disease-causing genes, although they might be risk factors, might modify disease, and/or might influence progression of disease. In addition, β -AR polymorphisms might influence drug responses (Table 6).

The β_2 -AR variations Gly¹⁶Arg and Gln²⁷Glu and, more recently, haplotypic variations, have been the focus of numerous pharmacogenetic studies looking at responses to SABAs and LABAs in subjects with chronic airway obstruction [115]. Thus far, a consensus on the effects of β_2 -AR genetic variations has not been reached, although there does appear to be a reproducible adverse effect in subjects homozygous for Arg¹⁶ that are regularly treated with SABAs [115]. The complexity of the genotype by response effects observed makes clinical application of β_2 -AR genetic variations limited, and may require the use of detailed haplotypic variation to fully understand the role that β_2 -AR plays in regulating β -agonist response [115].

Studies have examined whether the Ser⁴⁹Gly or Arg³⁸⁹Gly β_1 -AR polymorphisms influence responses to β -blockade during CHF treatment. Apparently, a better response to these drugs is observed in individuals with the Gly⁴⁹ variant [116]. On the other hand, *in vitro* and *ex vivo* results from the heart that showed that the Arg¹⁶Gly and Gln²⁷Glu β_2 -AR polymorphisms exert little influence on the functional activity of β_2 -AR. When investigating the association between the treatment efficacy of β -blockers in CHF patients and β_2 -AR polymorphisms, most studies failed to detect a positive association [117].

Further studies must confirm or deny that β -AR polymorphisms might affect drug responsiveness because this might lead to a more individualized drug therapy.

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Table 1 – Summary of some pharmacological properties of selected β_2 -agonists

β_2 -agonist	Affinity for β_2 -AR (K _i , nmol/L)	Efficacy at β_2 -AR (a)	Potency at β_2 -AR (b)	Selectivity ratio (β_1 -AR/ β_2 -AR)	Intrinsic efficacy (%)	Approximate onset of action (min)	Approximate duration of action
Isoprenaline	200	(100)	(1)	1/1	100	2-5	<20 min
Salbutamol	2500	88	1/120	1/1375	4.9	2-3	4-6 h
Fenoterol	ND	100	ND	1:120	42	2-4	4-6 h
Terbutaline	ND	65-85	ND	ND	ND	2-4	4-6 h
Salmeterol	53	63	8.5	1/85000	<2	30	>12 h
Formoterol	76	100	20	1/120	20	2-3	>12 h

a Relative to isoprenaline as 100%.

b Relative to isoprenaline.

ND = no data available.

Table 2 – β -blockers in CHF

- Acutely depress myocardial function (pharmacological)
- Chronically improve myocardial function (biological)
- Chronically reduce mortality by 30 – 65%
- Chronically reduce hospitalizations, MI and sudden cardiac death.
- Start with low dose and increase dose very slowly (months) to tolerable and effective dose. Some patients get worse before they start to improve.
- Not recommended in patients in Class I or IV.
- Contraindications:
 - Shock
 - Significant heart block without pacemaker
 - Severe bronchospastic pulmonary disease
- Not contraindications:
 - COPD
 - Diabetes
 - Asymptomatic bradycardia
 - Mild asthma

Table 3 – Pharmacological characteristics of β -blockers

Nonselective (β_1 - + β_2 -AR) (-ISA)	Nonselective (β_1 - + β_2 -AR) (+ ISA)	More selective for the β_1 -AR (- ISA)	More selective for the β_1 -AR (+ ISA)
Propranolol	Oxprenolol	Atenolol	Celiprolol (+ α - block)
Timolol	Pindolol	Metoprolol	Acebutolol
Nadolol	Dilevalol	Bisoprolol	Xamoterol
Sotalol (antiarrhythmic)	Prenatelol	Esmolol	
Ibutmonide (+ α - block)	Labetalol (+ α - block)	Practolol	
Carvedilol (+ α - block)	Carteolol	Pafenolol	
		Tolamolol	
		Bevantolol (+ α - block)	
		Nebivolol	

Table 4 - Impact of different classes of β -blockers on airways in patients with COPD

Drugs	Effect on Airway Function	Effect on the Bronchodilator Response to Inhaled β_2 -Agonists
Nonselective β ($\beta_1 + \beta_2$)-blockers	↓↓↓	↓↓↓
β_1 -selective blockers	↓	0/↓
Nonselective β -blockers with ISA	↓↓	↓↓
More selective for the β_1 -AR blockers with mild β_2 -agonist properties	0/↓	0/↓
More selective for the β_1 -AR blockers that modulate the endogenous production of NO	0/↓	0/↓

↓ = mild decrease; ↓↓ = moderate decrease; ↓↓↓ = severe decrease; 0 = no change

Table 5 - β -blockers for CHF

Drug	β -AR selectivity	Starting Dose	Target Dosage
Bisoprolol	It is 120-fold more selective for the β_1 -AR compared with β_2 -AR in humans	2.5 mg/day	10mg/day
Carvedilol	In addition to blocking β_1 - and β_2 -ARs, it also blocks α_1 -ARs and has antioxidant and antiendothelin properties	6.25 mg/day	50 mg/day (100 mg/day if >85 kg)
Metoprolol	It is 75-fold more selective for the β_1 -AR compared with β_2 -AR in humans	12.5-25mg/day	200mg/day

Table 6 – Effect of gene polymorphisms on the pharmacological treatment of COPD and CHF

β₁-AR Polymorphism	
Arg ³⁸⁹ Gly (Arg to Gly switch at codon 389)	Arg ³⁸⁹ β ₁ -AR is three to four times more responsive to agonist-evoked stimulation than Gly ³⁸⁹ β ₁ -AR Responses to β ₁ -AR blockers are larger in subjects homozygous for Arg ³⁸⁹
Ser ⁴⁹ Gly (Ser to Gly switch at codon 49)	Ser ⁴⁹ β ₁ -AR has decreased agonist-promoted downregulation and decreased adrenergic coupling Gly ⁴⁹ β ₁ -AR variant is linked to greater benefit from β ₁ -AR blockade
β₂-AR Polymorphism	
Arg ¹⁶ Gly (Arg to Gly switch at codon 16)	Gly ¹⁶ β ₂ -AR has greater agonist-promoted downregulation Larger vasodilation in subjects homozygous for the Arg ¹⁶ β ₂ -AR No reported interactions with β-blockers
Gln ²⁷ Glu (Gln to Glu switch at codon 27)	Glu ²⁷ β ₂ -AR is resistant to receptor downregulation
Thr ¹⁶⁴ Ile (Thr to Ile switch at codon 164)	Ile ¹⁶⁴ β ₂ -AR presents loss of function, decreased agonist binding, decreased cAMP

Arg = arginine, Gln = glutamine; Glu = glutamic acid; Gly = glycine, Ile = isoleucine, Ser = serine, Thr = threonine