Review

Inhaled beta2-agonists and beta-blockers in patients with chronic obstructive pulmonary disease and cardiovascular comorbidities: therapeutic dilemmas, myths and realities

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SUMMARY. Chronic obstructive pulmonary disease (COPD) has been shown to be associated with increased risk for cardiovascular events. The wide distribution of beta-adrenergic receptors in the respiratory and cardiovascular systems frequently discourages clinicians from using beta-blockers in patients with COPD or inhaled beta2-agonists in those with cardiovascular comorbidities. Evidence in the current literature suggests that inhaled short- and long-acting beta2-agonists can be considered safe in patients without significant cardiac disease or with clinically stable disease (arrhythmia, coronary artery disease or heart failure). In these situations COPD treatment should be initiated or adjusted rationally, provided that worsening of respiratory symptoms is not associated with decompensated heart failure or an acute coronary event. Cardioselective beta-blockers in usual doses should not be withheld from patients with COPD who have mild to severe airway obstruction, in whom their definite therapeutic benefits in the management of myocardial infarction and chronic heart failure outweigh the danger of possible induction of bronchospasm. Further research is necessary on the safety of beta-blockers in very severe stages of COPD (FEV_1 <30% pred.) and the use of non-cardioselective beta-blockers in subjects with partially reversible airway obstruction. ***Pneumon 2013, 26(1):59-74.***

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD) have a two- to threefold higher risk of cardiovascular disease compared with the healthy population[1,2]. Cardiovascular disease is the leading cause of hospital attendance and mortality in patients with mild and moderate COPD, in contrast with respiratory infections and COPD exacerbations that predominate in the severe stages[1,3,4]. Despite the frequent coexistence of common risk

factors such as smoking, advanced age and sedentary lifestyle, impaired respiratory function is independently associated with cardiovascular morbidity and mortality[5]. At the theoretical level, systemic inflammation, hypoxia, autonomic nerve dysfunction (increased sympathetic stimulation) and haemodynamic abnormalities have all been implicated in the systemic effects of COPD and its exacerbations, to the detriment of the cardiovascular system[6,7].

The clinician is therefore very often required to adjust medical treatment in patients with stable or exacerbated COPD and coexisting morbidities such as cardiac arrhythmia, coronary artery disease and heart failure (HF) and, vice versa, to address cardiac emergencies in patients with COPD whether under treatment or not. As described in detail below, beta-adrenergic receptors are widely distributed in the respiratory and cardiovascular systems and participate in both normal and pathogenetic mechanisms. The use of systemically administered or locally acting (inhaled) drugs targeting beta-receptors, with varying degrees of systemic absorption and selective action on the heart and lungs, has sometimes generated questions about the danger of pharmacological actions beyond the intended therapeutic effects.

BETA-RECEPTORS IN THE LUNG AND THE CARDIOVASCULAR SYSTEM: PATHOPHYSIOLOGICAL MECHANISMS AND ACTIONS

Beta-adrenergic receptors are divided into three subtypes: beta1, beta2 and beta3. The beta2-adrenergic receptors are the dominant subtype in the lung, where they exhibit a broad distribution that includes airway smooth muscle, macrophages, neutrophils, eosinophils, lymphocytes, epithelial and endothelial cells, type II pneumocytes and mast cells[8]. Binding of a molecule of a beta2-adrenergic agonist to the extracellular portion of the receptor leads to the activation of the intracellular enzyme adenylate cyclase, a process mediated by a tripartite protein of the Gs-class[9]. Increased levels of intracellular cyclic AMP (c-AMP) then catalyze the activation of protein kinase A and reduce the levels of intracellular Ca^{2+}, through mechanisms involving the transmembrane influx and intracellular stores of Ca^{2+}. This is the main pathway through which beta2-adrenergic receptors produce their bronchodilatory effects[8] (Figure 1A). In addition, the stimulation of presynaptic beta2-receptors located on the cholinergic nerves that innervate the large airways inhibits the release of acetylcholine, a potent bronchoconstrictor, thereby enhancing bronchodilation. Activation of beta2-receptors has been shown *in vitro* to be associated with anti-inflammatory effects, through inhibition of processes such as cellular activation and release of mediators, cell adhesion, chemotaxis and cell survival. The protective role against inflammation has also been confirmed *in vivo* in animal models, but the data available on patients are relatively limited and conflicting, and focus on inflammation in asthma rather than in COPD. Concerning most of the receptors whose actions are mediated via G-proteins, prolonged exposure to beta2-stimulating agents predisposes beta2-receptors to desensitization, which leads to down-regulation or tolerance. The resulting decrease in adrenergic response mainly affects anti-inflammatory activity[10], while bronchodilation is relatively resistant to the development of tolerance[11]. Conversely, a possible involvement of the chronic inflammation of COPD in the expression of beta2-receptors and the G-protein-adenylate cyclase system cannot be excluded.

The normal heart contains all three subtypes of beta receptors (beta1, beta2, beta3). Beta1 and beta2-receptors are present in a ratio of 60-80%: 40-20%, depending on their location in the atria or the ventricles[12,13]. Activation of cardiac beta-receptors leads to an increase in myocardial contractility (positive inotropic effect), heart rate (positive chronotropic effect), myocardial relaxation rate (positive lusitropic effect) and conduction velocity of electrical impulses through the AV node (positive dromotropic effect). Coupling of the stimulated receptor with intracellular pathways is mediated by Gs-class proteins, which enhance beta1 and beta2-adrenergic activity through increased c-AMP synthesis, and by Gi-class proteins, which desensitize beta1 activity. The final step in the Gs pathway is the activation of protein kinase A, which affects the function of transmembrane Ca^{2+} channels, ATP-dependent Ca^{2+} pumps on the sarcoplasmic reticulum, membrane channels of cardiac pacemaker cells and the Na^{+}/K^{+}-ATPase pump[14] (Figure 1B). In chronic HF, long-standing activation of the sympathetic nervous system contributes, through beta-adrenergic stimulation, to adverse cardiac remodeling, namely cardiac hypertrophy, fibrosis and apoptosis. At the same time, however, other potentially protective mechanisms may be activated, such as compensatory decrease in the number of beta1 receptors and subsequent increase in the proportion of beta2-receptors, uncoupling of beta1-receptors from the Gs-type proteins and desensitization of receptors through the Gi pathway which is induced by beta2-adrenergic

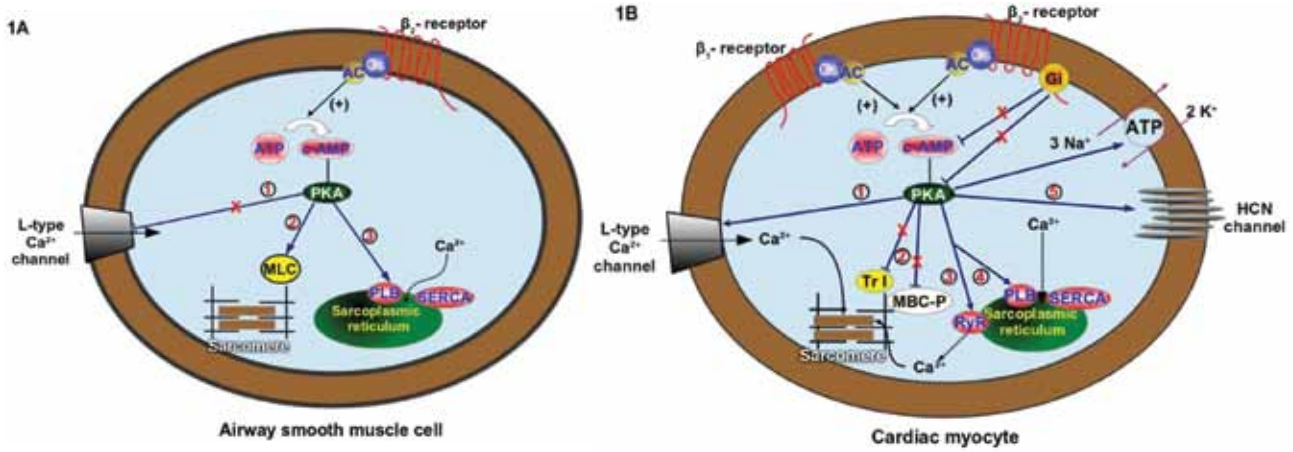

FIGURE 1. Major intracellular effects of beta-adrenergic receptor stimulation in airway smooth muscle cells and cardiac myocytes. **1A:** Beta2-receptor stimulation in airway smooth muscle cells causes relaxation through the cAMP-PKA pathways. PKA-mediated phosphorylation of the L-type Ca^{2+} channels and the PLB-SERCA complex leads to a decrease in the intracellular levels of Ca^{2+} (Pathways 1 and 3), while phosphorylation of the myosin light chains (MLC) reduces their Ca^{2+} sensitivity (Pathway 2). **1B:** Stimulation of cardiac beta1-receptors activates only Gs-class proteins, while beta2-receptors may be coupled with both Gs-class and Gi-class proteins. The Gs protein complex induces the adenyl cyclase (AC) enzyme, while the Gi complex has an inhibitory effect. AC causes an increase in cAMP production and the cAMP-dependent protein kinase A (PKA) is subsequently activated. Phosphorylation of target molecules by PKA may increase the intracellular levels of Ca^{2+} (Pathways 1 and 3) (positive inotropic and dromotropic effect), accelerate Ca^{2+} reuptake by sarcoplasmic reticulum or relaxation of myofilaments (Pathways 2 and 4) (positive lusitropic effect), or affect the initiation and modulation of rhythmic activity in cardiac pacemaker cells through the hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Pathway 5) (positive chronotropic effect). Tr I: Troponin I, MBC-P: Myosin binding protein-C, RyR: Ryanodine receptor, PLB: Phospholamban, SERCA: Sarco/endoplasmic reticulum Ca^{2+}- ATPase.

stimulation[15]. In this chronic stage, therefore, cardiac function is clearly dependent on the effective functioning of beta2-receptors.

CATEGORIES OF INHALED BETA2-AGONISTS USED IN THE TREATMENT OF COPD

Short-acting inhaled beta2-agonists (SABAs) are commonly used on demand by patients with both stable and exacerbated COPD [Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) Guidelines 2011][16]. The chief representatives of this category are salbutamol (racemic albuterol) and terbutaline, with onset of action within 2-4 minutes and a total duration of action of 4-6 hours[17]. Long-acting beta2-agonists (LABAs) are the cornerstone of treatment for patients with COPD belonging to the risk groups B to D, either as a single therapy or in combination with other drugs. Long-term administration of LABAs ameliorates dyspnoea, improves quality of life, reduces the frequency and severity of exacerbations and improves indices of lung function, hyperinflation and exercise capacity, but has no effect on either mortality or the natural course of the disease (GOLD Guidelines 2011). LABAs include the widely used formoterol and salmeterol, with time to onset of action of 2-3 minutes and 30 minutes respectively and total duration of action >12 hours each, and the newer generation indacaterol with a 24-hour duration of action[17,18]. The adverse cardiovascular effects of SABAs and LABAs may depend on the drug dose, the degree of systemic absorption, the beta2-adrenergic potency, the time to onset of action, the total duration of action and the duration of drug administration (Table 1).

INHALED BETA2-AGONISTS AND CARDIOVASCULAR COMORBIDITIES

Arrhythmogenesis

An early report on a study of continuous 24-hour electrocardiographic (ECG) (Holter), in hospitalized patients with COPD documented arrythmia at a rate close to 90%, 57% of which needed intervention[20]. The most frequently observed recordings of arrhythmia include ventricular premature beats (VPBs) (single, in bigeminy or in couplets),

TABLE 1. The major pharmacological properties of beta2-agonists[17,19].

	Average dose		Onset of action	Duration of action	Beta1/Beta2 selectivity ratio	Beta2 adrenergic	
	Once	Daily	minutes	hours		Potency	Intrinsic efficacy
SABAs							
Salbutamol							
MDI/Neb	200μg/2.5mg	x3-x4	2-3	4-6	1/1375	+	+
Terbutaline							
MDI	0.5mg	x3-x4	2-4	4-6	-	-	-
LABAs							
Salmeterol							
DPI/MDI	50μg/42μg	x2	30	>12	1/85000	+++	++
Formoterol							
DPI/MDI	12μg/9μg	x2	2-3	>12	1/120	++++	++++
Indacaterol							
DPI	150-300μg	x1	5	>24	1/24	++	+++

-: information not available
SABAs: Short acting beta2-agonists, LABAs: Long acting beta2-agonists, MDI: metered dose inhaler, DPI: dry powder inhaler, Neb: nebulizer

atrial premature beats (APBs) or other supraventricular premature beats, sinus and multifocal atrial tachycardia, while less frequent recordings include atrial fibrillation/flutter (AF/AFL), 'non-sustained' ventricular tachycardia and occasionally 'sustained' ventricular tachycardia (VT) and ventricular fibrillation[21,22]. The arrhythmogenic effects of inhaled beta2-agonists stem from the direct stimulation of myocardial beta2-receptors, which exert a positive chronotropic action and affect depolarization and repolarization of the myocardial cell and potassium (K) distribution[23]. These effects may be further amplified by concomitant hypoxaemia and acidaemia[24], underlying heart disease, autonomic dysfunction and QTc-prolongation[7,25]. The single or double-blind randomized studies assessing the arrhythmogenic effects of beta2-agonists in comparison with placebo have been heterogeneous in terms of the recording methods: clinical assessment, ECG or 24-hour recording (Holter), the numbers of participating patients and the initial design. This review includes studies in which the diagnosis of arrhythmic disorders has been documented by instant or 24-hour ECG recordings (Table 2).

Studies on inhaled SABAs have focused mainly on the effects of a single administration of the drug to patients with moderate to very severe stable COPD. The types of arrhythmia most commonly observed in instant or 24-hour ECG recordings have usually been clinically insignificant (sinus tachycardia, APBs, single VPBs) and rarely potentially fatal (e.g., VT)[26–28]. Few clinical trials conducted to date have demonstrated a statistically significant difference compared to placebo; this occurred mostly when the single doses used were higher than usual[28] and/or when the systematic use of the drug had been prolonged (>1 month)[29]. The small number of individuals with clinically significant cardiac disease included in these studies reduces their power. The administration of SABAs in this category of patients cannot, therefore, be considered safe, unless it is of short duration and does not exceed the usual single dose.

The majority of clinical trials on the efficacy of inhaled LABAs (salmeterol[30–34], formoterol[35–41] or indacaterol[42–49]) compared with placebo, recorded cardiova scular safety data derived from the simple ECG. The exclusion criteria reported in the methods section of these studies usually included clinically significant or unstable cardiac disease (arrythmia, coronary artery disease, HF). Most of the studies agreed on the absence of differences in the incidence of clinically significant arrhythmia[30–32,34,35,37,40,41] and/or QTc-prolongation[33,36,38,39,42–49] in subjects treated with LABAs compared with placebo. The QTc interval rarely (<2%)[45–49] exceeded the critical (according to some authors[50]) threshold of 500msec, which is associated with an increased risk of sudden death, while, more frequently (up to 16%)[36,42–44,46], it exceeded the upper normal limit of 470msec for women and 450ms for men, as defined

TABLE 2. 24-hour Holter electrocardiographic (ECG) findings in studies comparing beta2-agonists with placebo

			Study Characteristics					Arrhythmic Events				
								iHR	APBs	AF/SVT	VPBs*	
Inhaled drug	**First author Year**	**Study design**	**Participants(n) completing study (%)**	**Stage of COPD**	**Cardiac history**	**Form of inhalants**	**Dose *duration***	**Yes-No Frequency (%) Compared to PL (p-value)**				**VT$**
Salbutamol	Hall IP[26] 1994	SALB vs PL	22/100%	III	Ischemia in initial ECG (36%)	Neb.	5mg x4 24 hours	-	-	Yes 41 ns	Yes 41 ns	No
Salmeterol	Cazzola M[23] 1998	SALM vs L vs H-FORM vs PL	12/100%	III-IV	Mild-moderate arrhythmia	-	50µg x1	Yes - Sig	Yes 92% ns	-	Yes 50%/0% -	No
	Mahler DA[56] 1999	SALM vs IB vs PL	411/88%	II-III	-	-	42µg x2 3 months	No	Yes - ns	-	Yes - ns Less frequent than PL	No
	Mahler DA[57] 2002	SALM vs ICS vs SALM/ICS vs PL	691/66%	II-III	None	DPI	50µg x2 6 months	No	-	-	Yes - ns	No
	Hanrahan JP[22] 2008	ARFORM vs SALM vs PL	1178/81%	II-IV	CAD (9%) Arrhythmia History: 5% Holter: 40%	MDI	50µg x2 3 months	No	-	Yes 64% ns	-	Yes 10%/<2% ns
Formoterol	Cazzola M[23] 1998	L vs H-FORM vs SALM vs PL	12/100%	III-IV	Mild-moderate arrhythmia	-	12µg-24µg x1	Yes - Sig	Yes 100% ns	-	Yes 50 vs 58%/16 vs 25% -	No
	Nelson H[54] 2007	FORM vs PL	288/82%	II-III	None	MDI vs Neb	12µg/20µg x2 *3 months*	No	-	Yes 3.3% ns	Yes - ns	Yes 11.3% ns
	Campbell SC[53] 2007	FORM vs PL	204/92%	II-III	CAD Proarrhythmia (4%)	DPI	12µg x2 2 months	No	Yes >90% ns	Yes <1% ns	Yes - ns	Yes <5%/<1% ns
	Rennard SI[58] 2009	FORM/L-ICS vs FORM/H-ICS vs FORM vs PL	1964/69%	II-III	AF, HF (17.7%)	pMDI DPI	9µg x2 *3 months*	No	-	Yes <1% ns	-	-

iHR: increase in Heart Rate, APBs: Atrial Premature Beats, AF: Atrial Fibrillation, SVT: Supraventricular Tachycardia, VPBs: Ventricular Premature Beats, VT: Ventricular Tachycardia, SALB: Salbutamol, PL: Placebo, SALM: Salmeterol, IB: Ipratropium bromide, FORM: Formoterol, ARFORM: Arformoterol, L-, H-: Low, High dose, ICS: Inhaled Corticosteroids, CAD: Coronary Artry Disease, HF:Heart Failure, Sig: statistically significant result, ns: statistically non-significant result, (-): absence of data in the corresponding field

* Single VPBs /complex VPBs (couplets, ventricular bigeminy, ventricular trigeminy, multiform VPBs) $ Total incidence of VT/ 'sustained'VT (>10 consecutive VPBs)

by other authors[51,52]. Some of the few studies in which a 24-hour Holter recording was used, also included clinically stable patients with a known history of arrhythmia or arrhythmia diagnosed during the initial Holter recording (prior to randomization). A high single dose of formoterol (24μg) in this group of patients, with the coexistence of hypoxaemia, was implicated in the emergence of complex VPBs (ventricular bigeminy or multiform VPBs) at a rate of 25% and a trend towards an increase in the number of VPBs per 24-hour period compared with salmeterol (50μg x1), single low-dose formoterol (12μg) or placebo[23]. Due to the small size of the population (12 participants), the effect of formoterol and the degree of involvement of COPD (through hypoxaemia) in the observed outcome could not be substantiated with certainty. Two subsequent larger studies on the cardiac safety of long-standing (2-3 months) administration of formoterol in the usual daily dose (12μg x2), documented VT rates of 5%[53] and 11.3%[54] respectively, while 'sustained' VT was reported in less than 1% of the population of the first study[53]. In no case was any statistically significant difference from placebo documented, while in the first study some of the patients had a history of arrhythmia or coronary artery disease. Focusing on the development of arrhythmia in patients with COPD and the possible role of inhaled LABAs, Hanrahan and co-workers[22] found similar incidences of 'sustained' and 'non-sustained' VT in a population diagnosed with various types of arrhythmia on the initial baseline Holter prior to treatment (VT up to 5.7%), without being able to establish an independent role for inhaled salmeterol. A major meta-analysis in 2003[55], conducted to investigate the cardiovascular safety of salmeterol (50μg x2) compared with placebo in patients with COPD, included data from 7 studies that used instant ECG recordings and 3 studies that used 24-hour ECG recordings. No difference was observed between salmeterol and placebo regarding the recording of clinically significant ECG changes, heart rate, APBs, single and complex VPBs, or QTc alterations, while no episode of VT appeared in the Holter recordings. In conclusion salmeterol and formoterol have been shown to be safe when administered in the usual doses to patients with known stable arrhythmia, while for indacaterol, further safety studies using 24-hour Holter recording are required. Regular monitoring with Holter recordings may be indicated for stable patients with a history of more serious arrhythmia (complex VPBs, VT or supraventricular tachycardia with haemodynamic instability or concomitant HF) and when using single doses of formoterol that exceed 12 μg.

Heart failure

The extent to which the use of inhaled beta2-agonists increases the risk for HF or affects the risk of hospitalization of patients with known chronic HF has not yet been clarified. Only a few large studies have focused their analysis on the effects of inhaled SABAs and LABAs in patients with COPD and coexistent HF. Two large studies conducted by Au and co-workers[59,60] in patients with known systolic HF (EF <45%), who had systematically received inhaled beta2-agonists in the previous 3 months, demonstrated an increase in the risk of hospitalization for worsening HF that was correlated with the monthly consumption of the drug (number of canisters) in a dose-dependent manner. Similarly, in 2008, an analysis of a large respiratory disease database over a 5-year period in one province of Canada (Manitoba)[61], showed that long-term use of beta2-agonists was associated with an increased risk of hospitalization for HF. The above studies do not clearly distinguish between categories of inhaled medications (SABAs or LABAs) and, even though the demonstrated correlation was independent of the presence of COPD or other comorbidities, it does not necessarily substantiate an aetiopathogenetic role for beta2-agonists. It is possible that the aggravation of dyspnoea that led to increased consumption of inhaled drugs was due to worsening chronic HF rather than to COPD. A meta-analysis by Salpeter and co-workers[62] which included 20 single or double-blind randomized studies in patients with COPD or asthma, concluded that the long-term use of LABAs increases, though not to a statistically significant degree, the risk for major cardiovascular events (VT, VF, syncope, congestive HF, AMI, cardiac arrest or death). Shortcomings of that study include the absence of a subanalysis for the COPD group or separate analysis on the outcome of HF, and the significant heterogeneity in size, duration and incidence of the recorded cardiac events among the included trials. A possible explanation of the above effects of the chronic use of beta2-agonists might lie in the desensitization and down-regulation of myocardial beta2-receptors due to prolonged stimulation and in the activation of Gi system that down-regulates the Gs-dependent cardiac contraction[63,64].

Systemically administered beta2-agonists are known to cause a transient improvement of cardiac function in patients with decompensated HF, as they enhance stroke volume and other cardiac markers[65,66], but the effect of inhaled beta2-agonists has not been studied prospectively in this patient group. Indirect evidence has been

derived from small studies on the acute administration of nebulized SABAs (albuterol, terbutaline) in patients with chronic HF[67–69] and, occasionally, coexisting COPD[70]. These studies described an improvement in lung function indices (increase in FEV_1, PEF, decrease in airway resistance) and haemodynamic parameters (increase in the ejection fraction and cardiac index, reduction of systolic and diastolic blood pressure) following the administration of SABAs. However, it is worthy of note that a large nationwide registry of patients with acute HF demonstrated that 14% of patients presenting with dyspnoea were treated for COPD, although no COPD was present and their dyspnoea was subsequently found to be due to HF. In addition, the use of inhalants in these patients was associated with an increased risk of clinical deterioration and need for intravenous vasodilators and mechanical ventilation, but withno increase in mortality[71].

The use of beta2-agonists, therefore, in the symptomatic treatment of dyspnoea should be considered judiciously and initiated only after the cause of dyspnoea has been investigated and airway obstruction has been objectively documented. Furthermore, before any modification of the long-term treatment of patients with chronic HF and coexistent COPD, it is necessary to consider the possible contribution of worsening chronic HF to the exacerbation of symptoms.

Coronary artery disease

The association of inhaled beta2-agonists with an increased risk of acute coronary syndrome (unstable angina and/or fatal or nonfatal acute myocardial infarction) has been supported by case-control studies that drew their information from medical databases on the general population and the medical records of major hospital units. The earliest of these studies concluded that recently initiated (during the last 3 months), single use of beta2-agonists increases about 7-fold the risk of myocardial infarction, but only in patients with a known cardiac history[72]. That analysis was not weighted according to the presence of respiratory disease (COPD or asthma), while the distribution of COPD in the case and control groups was not described clearly. Suissa and colleagues[73] argued that the increased risk observed may reflect the recent use of inhalants for the alleviation of symptoms which were due to coronary artery disease (dyspnoea, chest pain) and not to true obstructive lung disease. Among 6,463 patients from 7 medical centres[74], the risk of unstable angina or myocardial infarction was increased in those receiving inhaled beta2-agonists by metered dose inhaler (MDI) within the last 3 months in a dose dependent manner [OR (95% CI): 1.38 (0.86-2.23) for one to two canisters, 1.58 (1.01-2.46) for three to five canisters and 1.93 (1.23-3.03) for six or more], independently of other clinical characteristics, the presence of cardiovascular comorbidities or COPD. The risk was increased further when the analysis was confined to the subgroup of patients who were not receiving beta-adrenergic blockers systematically. Additionally, analysis of the data from the medical records of Manitoba[61] showed that the risk of hospitalization for myocardial infarction was correlated with the use of inhaled beta2-agonists during the previous 2-month and 1-year periods. Although the individual contribution of COPD to the increased risk was not specified, in a multivariate analysis including any respiratory (COPD, asthma, bronchitis) or other comorbidity and the use of cardiac and other medications, the relative risk was decreased, but remained statistically significant [(OR (95% CI): 1.46 (1.32-1.61) vs 1.31 (1.15-1.51) for 2 months and 1.33 (1.22-1.44) vs 1.15 (1.02-1.29) for 1 year].

The possible interpretations of the above findings are summarized in the aetiopathogenetic involvement of inhaled beta2-agonists in inducing myocardial ischaemia on the one hand and the possibility of a non-causal relationship on the other. Beta2-adrenergic stimulation due to the systemic absorption of the inhaled drug exerts simultaneous chronotropic, inotropic and arrhythmogenic effects on the myocardium and therefore, particularly in patients with preexisting coronary artery disease, may induce ischaemia and myocardial infarction. Ischaemic conditions can be further intensified by hypoxaemia, which may be aggravated by beta2-agonists via the mechanism of ventilation-perfusion mismatch. Conversely, unstable angina, which is the prelude to myocardial infarction, may actually have been the underlying cause of non-specific respiratory symptoms or chest discomfort that urged the patients to use inhalants. Due to the fact that some of the studies did not weight their results according to the presence[72] or the severity of COPD[61,74], it was not possible to preclude the co-liability of the underlying COPD in the non-improvement of hypoxaemia (despite the intense use of bronchodilators) or the induction of myocardial ischaemia.

The first study to negate the potential provocation of acute coronary episode included 24 patients with a history of coronary artery disease who received single increasing doses of salbutamol (up to 0.8mg) in the form of MDI or one dose of 5mg in nebulization[70]. This was a study of a mixed population of patients with stable obstructive lung

disease (COPD, asthma), the majority of whom (20/24) were not on beta-blockers at the time of the study, but there was no control group to compare with the use of placebo. The safety of SABA administration in patients with obstructive disease was supported more thoroughly in a later study by Suissa and colleagues[73] that included a large number of patients with COPD (n=12,090). The use of short-acting beta2-agonists in any form (tablets, nebulization, MDI), current, or recently introduced, or within the last year, did not increase the relative risk for fatal or non fatal myocardial infarction to a statistically significant degree. The results did not change when the analysis was stratified by the presence of cardiovascular disease or risk factors or beta- blocker use. The non-significant trend for increase in risk by a ratio of 11% for every 10 canisters used during the last year, may possibly reflect the contribution of severe airway obstruction, but there were insufficient data regarding the stage of COPD in this population. The severity of COPD, as evidenced by the number of hospitalizations during the preceding 12 months and the prescription of inhaled corticosteroids, was included in the analysis of the risk for non fatal myocardial infarction in a population of hypertensive patients[75]. Provided that a low cumulative dose of inhaled bronchodilators (SABAs or LABAs) had been received, it was demonstrated that treatment with beta2-agonists of recent onset (within 3 months) increases relative risk only in the group of patients with a history of ischaemic heart disease.

In conclusion, it appears that prolonged (>1 year) treatment with beta2-agonists in patients with or without a known cardiac history is safe regarding the risk for acute coronary events. Despite the disagreement observed among studies, the clinician's attention should be focused on the initial period of treatment (the first 3 months) in patients with known ischaemic heart disease, and in cases where the symptoms attributed to COPD do not respond to the usual doses of bronchodilators, as this may indicate an acute coronary event. Finally, the need for appropriate adjustment of treatment in patients with advanced COPD is emphasized, as severe obstruction is independently associated with an increased risk of myocardial infarction[5].

BETA-BLOCKERS: CATEGORIES AND MAIN INDICATIONS

Beta-blockers can be classified in terms of the receptor type on which they act and their principal pharmacological properties. Some have beta1-receptor selectivity and are more likely to affect cardiac function (cardioselectivity). Non-cardioselective beta-blockers act on all beta-adrenergic receptors, causing bronchospasm or various other extracardiac effects, but occasionally stimulate alpha-receptors, causing coronary and peripheral vasodilatation. Selectivity is a dose-dependent phenomenon and diminishes when drug dosage exceeds a specific limit. Several beta-blockers may have an intrinsic sympathomimetic activity. Others, depending on their lipid solubility, may pass through cell membranes, penetrate the blood-brain barrier and induce adverse neurological and psychiatric effects such as depression, hallucinations and insomnia (Table 3).

Beta-blockers have long been established as agents for the treatment of cardiac disease, including left ventricular dysfunction and myocardial ischaemia. Their beneficial

TABLE 3. Pharmacological properties of the principal beta-blockers76.

Drug	Adrenergic-receptor blocking activity	Intrinsic sympathomimetic activity	Lipid solubility	Common daily dose
Acebutolol	β_1	Yes	+	400-1200 mg
Atenolol	β_1	No	+	50-100 mg
Bisoprolol	β_1	No	++	5-20 mg
Carvedilol	$\beta_1/\beta_2/\alpha_1$	No	+++	6,25-100 mg
Labetalol	$\beta_1/\beta_2/\alpha_1$	No	+	200-800 mg
Metoprolol	β_1	No	++	50-400 mg
Pindolol	β_1/β_2	Yes	++	10-40 mg
Propanolol	β_1/β_2	No	+++	80-320 mg
Timolol	β_1/β_2	No	+	20-60 mg
Nadolol	β_1/β_2	No	+	40-80mg

effects are exerted through various mechanisms, including bradycardia and reduction in myocardial oxygen consumption. According to the 2007 guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC), long-term administration of beta-blockers to patients with stable disease after myocardial infarction is indicated as a first line treatment for secondary prevention (Evidence A)[77]. Beta-blockers are also effective in HF, hypertension, various types of arrhythmia and cardiac thyrotoxicosis. Several HF studies have demonstrated that the use of beta-blockers is significant in reducing cardiovascular mortality, sudden deaths and hospital admissions, and in improving dyspnoea[78,79].

BETA-BLOCKERS AND COPD

Despite the plethora of studies that provide evidence for the compelling benefits of beta-blockers, less than 50% of patients studied had received optimal treatment on a long-term basis with maximum tolerated doses. This issue mainly concerned elderly patients and those with diabetes mellitus and COPD, who paradoxically, because of their comorbidity, could benefit the most from the use of beta-blockers[80–83]. Only 54% of patients with acute coronary syndrome were prescribed beta-blockers, as demonstrated by a recent retrospective study[84], where the presence of COPD was the most frequent reason for withholding treatment. Only 62% of those patients had a previous diagnosis of COPD on the basis of combined clinical and spirometric assessment, and 16% of the patients with COPD finally received beta-blockers. The unwillingness of clinicians to prescribe these agents in COPD is based on isolated cases and small series of patients[85–88] and is related mainly to concern about bronchospasm induction and lung function impairment through the effects of non-selective beta-blockers on pulmonary beta2-adrenergic receptors.

Beta-blockers in patients with coronary artery disease and COPD

According to Chen and colleagues[89], concomitant respiratory diseases such as COPD or asthma are the main reason for treatment interruption in elderly patients receiving beta-blockers after myocardial infarction. Their study demonstrated that patients with mild to moderate COPD, who did not use beta-agonists on a regular basis, have a significant reduction in overall mortality at one-year postinfarction, when treated with beta-blockers. An earlier publication of Gottlieb and colleagues[82] concluded that mortality decreased by up to 40% in postinfarction patients with COPD treated with beta-blockers. Subsequent analysis[90] of data generated from a population of 155,774 patients with recent myocardial infarction, 14% of which had obstructive airways disease, verified the results of earlier studies: A strong association was observed between beta-blocker administration within the first 24 hours of hospitalization and decreased in-hospital mortality, in patients both with and without reactive airway disease (COPD or asthma) [OR (95%CI): 0.52 (0.45-0.60), $p<0.001$ and 0.38 (0.34-0.42), $p<0.001$, respectively]. In view of the well-established beneficial effect of prompt initiation and continuation of beta-blocker treatment in the management of myocardial infarction, it is considered that beta-blockers should not be withheld from patients with COPD. It is recommended that treatment should be initiated in the safe hospital setting, under close observation for potential respiratory adverse effects[90]. The safe use of the beta1-selective blocker, metoprolol, even at maximum doses, has been corroborated by a study that included patients with COPD and stable or unstable angina[91].

Beta-blockers in hypertensive patients with COPD

A study published by Au and colleagues in 2004[92] compared the respiratory effects of beta-blockers and other antihypertensive drugs in a cohort of 1,966 patients with COPD and coexisting hypertension. They concluded that there was neither increase in respiratory exacerbations nor deterioration of lung function in the patients treated with beta-blockers. In addition, an all-cause mortality benefit was observed when beta-blockers, even at maximum dosage, were compared with calcium channel blockers. Comparison with other agents showed no statistically significant differences. A probable explanation of these findings is that beta-blockers may have a protective role against other cardiovascular events apart from regulation of arterial pressure.

An important meta-analysis by Salpeter and colleagues, published in 2005[93] focused on the effect of cardioselective beta1-blockers in the daily activity, respiratory symptoms, FEV_1 changes and bronchodilation response of patients with cardiovascular disease and coexisting COPD. This meta-analysis included 20 blinded, randomized studies, conducted from 1966 to 2000, of which 11 were single-dose studies[94–102] and the rest were of longer treatment duration, ranging from 2 days to 12 weeks[103–111]. They concluded that the use of cardioselective beta-blockers

is probably safe and well tolerated in patients with COPD. Cardioselective beta-blockers did not cause significant changes in FEV_1 or worsen respiratory symptoms in patients with COPD, when used either as a single dose or as long-term treatment. No significant effect on FEV_1 response was observed in 7 of the trials that included patients with reversible airway disease (FEV_1 reduction ranging from 1.26% to 1.8%), after either single-dose or long-term treatment with cardioselective beta-blockers[100–102,107,108,110], and post-bronchodilatory FEV_1 was increased by 15%. Six clinical trials included patients with severe airways obstruction (FEV_1 <1.4L or 50% pred.)[96,98,103,106,108,110]; a reduction in $FEV_1$of 10% was shown in two of the studies, while in the other 4 no significant change was reported (-0.71% to -3.11%) following beta-blocker administration. The absence of respiratory symptoms and FEV_1 stability, after either long-term or single-dose treatment, was confirmed by a specific analysis of 8 studies that included patients with comorbid angina or hypertension[97,99–101,103,104,109]. The relatively short duration of those studies (≤3 months) limits significantly to the possibility of drawing confident conclusions. Additional drawbacks were the small absolute number of patients in most studies and the fact that several of the studies were neither double-blinded nor placebo-controlled. Although beta-blockers do not have a clear indication for use in elderly patients with uncomplicated hypertension[112], the administration of cardioselective beta-blockers in patients with COPD and coexisting resistant hypertension or other cardiovascular disease is considered safe.

Beta-blockers in patients with chronic heart failure and COPD

Beta-blockers, particularly bisoprolol, the extended-release metoprolol succinate (both cardioselective without intrinsic sympathomimetic activity) and carvedilol (non cardioselective with alpha-blocking activity), are considered a cornerstone of the treatment of patients with impaired left ventricular ejection fraction, since it has been documented that these drugs improve survival across the whole spectrum of disease severity[113]. The vast majority of randomized clinical trials on the efficacy of beta-blockers in chronic HF, excluded patients with COPD, and in those in which they were included, they usually did not exceed 10% of the study population, which is far less than the prevalence of COPD described in patients with chronic HF, and they were treated with relatively low doses of beta-blockers[114].

The large meta-analyses published by Salpeter and colleagues[93,115–117], of studies on patients with mild, moderate[116] or severe COPD with or without reversibility of airflow limitation[93,115,117] produced the conclusion that short- or long-term (2 days to 12 weeks) use of cardioselective beta-blockers did not induce statistically significant change in FEV_1, bronchodilator response, respiratory symptoms or the frequency of exacerbations in comparison to placebo. None of the studies included in the meta-analysis, however, referred to patients with confirmed HF. Metoprolol and less frequently bisoprolol were administrated in most cases, while no study used carvedilol or nebivolol. In one of the few prospective, randomized clinical trials conducted in patients with concomitant chronic HF and COPD[118], 4-month administration of bisoprolol induced reduction of FEV_1 in comparison to placebo (-70vs+120mL, p=0.01), and improved symptoms and quality of life, but did not affect the magnitude of reversibility or the number of exacerbations. It should be noted that patients included in that study had moderate or severe stage COPD, while the average dose of bisoprolol (7.3 and 8.4mg, respectively) was within the usual range of dosage. As demonstrated by a subsequent randomized, non-blind study of 35 patients with COPD and chronic HF, bisoprolol was found to be superior to equivalent doses of carvedilol, regarding measurements of post-bronchodilator FEV_1 after 6 weeks of treatment [2.00 (1.79-2.22) vs 1.85 (1.67-2.03) L, p<0.01][119]. A larger study of patients with chronic HF without respiratory comorbidity showed the same outcome[120].

Documentation of the use of non selective beta- and alpha-adrenergic blockers such as carvedilol and labetalol is even scarcer. Although the use of carvedilol appeared to improve left ventricular ejection fraction in patients with chronic HF, it did not significantly affect the spirometric indices, static lung volume or carbon monoxide lung diffusion (DLCO)[121]. In a retrospective study of carvedilol tolerability in patients with chronic HF, 3-month stable-dose treatment was well tolerated in 85% of a subgroup of patients with concomitant COPD or asthma, but neither the reasons for interrupting drug administration, nor the proportion of patients that presented reversibility were clearly stated[122]. A 2-year follow-up study that included 31 patients with chronic HF and concomitant irreversible COPD treated with carvedilol (average daily dose 29±19 mg) demonstrated that the drug was better tolerated in this group than in patients with asthma[123]. Data on the safe use of carvedilol in patients with partially reversible COPD are lacking. One study[111] on patients with COPD raised concern about the acute increase in bronchial

hyperreactivity in the initial period of treatment with selective (metoprolol) or non selective beta-blockers (propanolol), although such effects were not observed in a murine model of asthma after long-term administration of carvedilol or nadolol[124]. A possible explanation of the above phenomenon might lie in the increase of beta2-receptor concentration in the bronchial tree after long-term exposure to beta-blockers.

The 2009 AHA guidelines for the management of chronic HF[113] recommend the use of beta-blockers in patients with reactive airway disease, provided that they are closely monitored. Meanwhile, COPD is not considered a contraindication for the use of beta-blockers by the European Society of Cardiology (ESC) guidelines[125]. In general, cardioselective beta-blockers without intrinsic sympathomimetic effect (metoprolol, bisoprolol, nebivolol) are regarded as preferable. An initial low-dose beta-blocker regime is recommended, with gradual increase of the dose (every 15 days) within the next 12 weeks. Early mild aggravation of respiratory symptoms or indices should not dictate the immediate interruption of treatment[114]. In addition, because of the current lack of data, special attention should be paid to the use of beta-blockers in patients with very severe COPD, and to the initial period of treatment in patients with reversible COPD[111].

Association of beta-blockers with mortality and the risk of exacerbation of COPD

Observational studies have associated the use of beta-blockers in patients with COPD and chronic HF with increased survival. The valsartan clinical trial in patients with chronic HF (Val-HeFT)[126] concluded that the risk of mortality was significantly decreased in 140 patients with concomitant COPD after the administration of beta-blockers for approximately 2 years (17% vs 31%, $p<0.001$). The beneficial association of beta-blocker use with a reduced risk of in-hospital death was also demonstrated in the study of Dransfield and colleagues[127] on patients hospitalized for acute exacerbations of COPD. In addition, a large cohort (n=2,230) study of COPD patients[128] demonstrated a potential survival benefit from beta-blockers [OR (95% CI): 0.68 (0.56-0.83)] and a reduced risk of exacerbations [OR (95% CI): 0.71 (0.60-0.83)], regardless of the presence of concomitant cardiovascular disease. Similar conclusions were drawn from a more recent retrospective study in a larger cohort of patients at different stages of COPD[129]. Further prospective studies are necessary in order to confirm the beneficial effects of beta-blockers.

CONCLUSIONS

The majority of studies that included patients without clinically significant heart disease, contain data that have established the safety of short and long-acting inhaled beta2-agonists, regarding the provocation of arrhythmia. When maximum doses of inhaled beta2-agonists are used in patients with a history of serious arrhythmias, however, even when they are clinically stable, regular ECG or Holter monitoring is highly recommended. Moreover, considerable attention should be given to patients with COPD patients and concomitant HF, as the deterioration of symptoms may require appropriate adjustment of treatment with beta2-agonists or may conceal heart failure progression. Finally, the need is emphasized for clinicians to focus their attention on the initial period of treatment with inhaled beta-agonists (i.e., the first 3 months) in patients with known ischaemic heart disease, and to exclude an acute coronary event that may masquerade as COPD exacerbation.

New prospective studies are needed to fill in the existing knowledge gaps regarding treatment strategies for patients with COPD receiving beta-blockers, since the current relevant data are mainly derived from meta-analyses. According to present documentation, the administration of cardioselective beta-blockers to patients with COPD is well tolerated and therefore this group of patients should not be deprived of their therapeutic benefits. The initiation of treatment in a hospital environment, with gradual dose increase up to the optimal and maximum tolerated levels is considered to be a safe approach. Patients with coronary artery disease are usually treated with beta1-selective blockers such as metoprolol, bisoprolol and atenolol. Since metoprolol has a short half-life, its administration appears to be safe and effective and can be used as the treatment of choice in patients with concomitant COPD[91]. The respiratory effects of nebivolol, a third generation cardioselective beta1-blocker with a nitric oxide potentiating vasodilatory effect, and its potential therapeutic benefits compared with other cardioselective beta-blockers need to be clarified by additional randomized clinical trials[130,131].

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