

# Long-acting $\beta_2$ -agonists (LABA) in chronic obstructive pulmonary disease: efficacy and safety

Andrea Rossi<sup>1</sup>  
Sonia Khirani<sup>1</sup>  
Mario Cazzola<sup>2</sup>

<sup>1</sup>Unit of Respiratory Diseases, Hospital of Bergamo, Bergamo, Italy; <sup>2</sup>Unit of Respiratory Diseases, Department of Internal Medicine, University of Rome 'Tor Vergata', Rome, Italy

**Abstract:** COPD is characterized by progressive airflow obstruction which does not fully reverse to inhaled or oral pharmacotherapy. The management of patients with COPD has taken a totally new direction over the past 20 years, thank to the use of novel therapies aimed to improve and modify the natural history of COPD. Long-acting bronchodilators, including long-acting  $\beta_2$ -agonists (LABAs), were introduced several years ago in order to enhance improvements in lung function, health status related quality of life, and reduce the rate of exacerbations. These effects can be boosted by the combination of LABAs with long-acting anticholinergic, and/or with inhaled corticosteroids. Inhaled LABAs are commonly well tolerated although adverse effects such as tremor and palpitations are occasionally troublesome.

**Keywords:** LABA, COPD, efficacy, safety

## Introduction

For many years, COPD has been defined as a disorder of airways (inflammation) and lung parenchyma (destruction) characterized by “poorly reversible” airflow limitation (American Thoracic Society 1995; Siafakas et al 1995). Airflow limitation is defined by a FEV<sub>1</sub>/FVC ratio < 0.7 post-bronchodilator (Pauwels et al 2001; Celli and MacNee 2004). However, bronchodilators were (and are) consistently reported as the “first-line treatment” of COPD, in patients with airflow limitation and symptoms (Pauwels et al 2001; Celli and MacNee 2004). There is an apparent contradiction between the “poorly reversible” label of the disease in the definition and the indication as “first-line therapy” of drugs whose major action is the reversibility of airflow obstruction through bronchial smooth muscle relaxation.

In fact, many recent studies have shown that significant reversibility of the airflow limitation can be detected in about half of patients with moderate-to-severe COPD recruited for clinical trials. Furthermore, it has been systematically observed that regular treatment of COPD patients with bronchodilators improve symptoms such as dyspnea and exercise tolerance (Rennard and Calverley 2006). In the more recent international documents (Celli and MacNee 2004), the expression “poorly reversible” has been replaced by “not completely reversible” and the definition has been reviewed such that now COPD is described as a “treatable and preventable” disease.

## From “negative” to “positive” approach

The new “positive” attitude toward COPD, leaving the “negative” (sometimes called nihilistic) approach to the past, is the result of many clinical studies, which have documented how pharmacologic and non-pharmacologic treatments for patients with moderate-to-severe COPD can be effective in improving the patient’s health status and in preventing exacerbations of the disease (Celli and MacNee 2004). As previously mentioned, several clinical trials have shown that some degree of reversibility of the airflow limitation is not uncommon in patients with COPD and that the regular treatment

Correspondence: Andrea Rossi  
A.O. Ospedali Riuniti di Bergamo,  
U.S.C. Pneumologia, Largo Barozzi, 1,  
24128 Bergamo (BG), Italia  
Tel +39 035 26 9714  
Fax +39 035 26 6825  
Email arossi@ospedaliriuniti.bergamo.it

with long-acting bronchodilators has favorable outcomes in those patients (Cazzola and Dahl 2004; Tashkin and Cooper 2004; Rennard and Calverley 2006).

The clinical studies failed to find any relationship between the acute and long-term response to inhaled bronchodilators. It is widely recognized that the change in FEV<sub>1</sub> after an acute bronchodilatation test does not predict either the long-term effect of the regular bronchodilating treatment nor the perception of improvement by the patients (Celli and MacNee 2004). Therefore, the “poor reversibility” of an acute bronchodilating test cannot be used to exclude patients from the benefits of long term treatment. It has been shown that the response to the bronchodilating therapy may develop after two weeks of treatment or even more. The guide for therapy is not the change in FEV<sub>1</sub>, but the relief from symptoms and particularly the reduction of dyspnea and the improvement in the exercise tolerance. The latter can be easily assessed not only by listening to the patients but also, at least for clinical purposes, by means of the 6 minutes walking test. This is a simple investigation, easy to perform in the clinical settings and approximately predictive of the patients’ exercise capacity. The grade of chronic dyspnea can be measured by means of the MRC (medical research council) scale (Celli et al 2004).

## Classes of bronchodilators

Among bronchodilators, short-acting agents, such as salbutamol, fenoterol, terbutaline, and ipratropium, have been abandoned for the regular therapy of COPD patients and are suggested only for rapid symptom relief as rescue medication. This approach has been adopted from the Asthma guidelines and becomes useful for COPD mainly when an exacerbation begins. Long-acting bronchodilators are indicated for regular treatment of symptomatic patients with moderate-to-severe COPD. The long-acting agents include two classes of drugs:

- the long-acting  $\beta_2$ -agonists (LABAs), eg, salmeterol and formoterol;
- the anticholinergics, eg, tiotropium.

Formoterol and salmeterol are both long-acting bronchodilators that are effective in the treatment of asthma (Lötvall 2001). After single doses, clear effects are maintained for 12 h after inhalation and with high doses, effects are observed even at 24 h. However, some differences exist in their pharmacology that are reflected in their clinical profiles. Formoterol has a rapid onset of action, whereas salmeterol causes bronchodilation in a somewhat slower manner. Moreover, formoterol has a higher intrinsic

activity than salmeterol, which means that it is a full agonist, whereas salmeterol is a partial agonist of  $\beta_2$ -adrenoceptor. Physicochemical properties of the drugs may explain the differences in onset and duration of action. Adequate water solubility and moderate lipophilicity of formoterol ensures rapid diffusion to the  $\beta_2$ -adrenoceptor on the smooth muscle and rapid bronchodilating activity. Salmeterol, on the other hand, may diffuse more slowly to the  $\beta_2$ -adrenoceptor because of its high lipophilicity, explaining the slower onset of action. Unlike salbutamol, which is hydrophilic and has a rapid onset and short duration of action, both formoterol and salmeterol possess adequate lipophilic properties to remain in the airway tissues as a depot in close vicinity of the  $\beta_2$ -adrenoceptors, explaining their long duration of effect. The long duration of salmeterol has also been suggested to depend on an anchored binding within the  $\beta_2$ -adrenoceptor.

The available data on LABA come from studies lasting 1 year or less (Man et al 2003; Sin et al 2003; Sutherland and Cherniack 2004). Only recently a 3-year prospective study (the TORCH study) has been published (The TORCH Study Group 2004; Calverley et al 2007). In that study, an arm was represented by therapy with salmeterol for 3 years. A longer study (4 years), namely the “Understanding Potential Long-Term Impacts on Function with Tiotropium” – UPLIFT, is still in progress, and the data will be available in 2008. This study is based on the long-acting anticholinergic agent, tiotropium (Rabe 2007). Another 4-year study was carried out some years ago on the short-acting anticholinergic agent ipratropium bromide (Anthonisen et al 1994). That study failed to show any effect of ipratropium bromide on the progression of COPD, measured by means of the annual decline of FEV<sub>1</sub>, compared with placebo.

In this article only LABAs are considered. LABAs are more effective with fewer side effects than theophylline (Rossi et al 2002). Theophylline was the common therapy for COPD before LABAs were introduced, though its use is still not negligible in western countries. Theophylline is still commonly used in some countries, mainly Asiatic, where for economic reasons it remains the preferred bronchodilator. A few studies encourage the association of LABA with theophylline (Rennard and Calverley 2006). However, the association of LABA with long-acting anticholinergics seems more promising (Cazzola et al 2004; Van Noord et al 2005; Van Noord et al 2006; Aaron et al 2007).

## LABAs in COPD

The role of long-acting bronchodilators, both LABAs and tiotropium, in the management of COPD is well established

and graded with evidence A in the national and international guidelines documents (Pauwels et al 2001; Kottakis et al 2002; Celli and MacNee 2004). In fact, several prospective randomized trials and a high quality meta-analysis (Man et al 2003; Sin et al 2003) have shown that LABAs improve lung function and health status related quality of life, and reduce exacerbations in symptomatic patients with moderate-to-severe COPD. The improvement in lung function, measured by means of the baseline change in FEV<sub>1</sub> is rather small, amounting on average to 100–150 mL. However, it is statistically significant and it is associated with an improvement in the patient's condition and health status perception. Moreover, LABAs have the potential to improve the mucociliary component of COPD. In combination with an inhaled corticosteroid, mucociliary clearance is indirectly improved by the presence of important anti-inflammatory activity (Rogers 2005).

The studies on LABAs up to 1 year failed to show any effect of the treatment on the progression of COPD, measured by means of the rate of decline of FEV<sub>1</sub>. Interestingly, all trials failed also to find any correlation between the improvement in symptoms and in FEV<sub>1</sub>. The lack of this relationship raises the question about the mechanism through which LABA can determine an improvement in the health status.

### **LABAs, airflow limitation, and pulmonary hyperinflation**

It is well known that smoking cessation modifies the natural history of COPD by reducing significantly the progressive decline in FEV<sub>1</sub> (Petty 2006) and even mortality (Anthonisen et al 2005). By contrast, LABAs improve lung function but do not reduce the faster annual rate of decline of FEV<sub>1</sub> in COPD patients compared with smokers without COPD and non-smokers (Man et al 2003; Sin et al 2003). This conclusion, coming from the 1-year or shorter clinical trials, has been challenged by the results of the TORCH study, which showed a greater rate of the decline of FEV<sub>1</sub> in the placebo arm compared with the salmeterol arm (The TORCH Study Group 2004; Calverley et al 2007). The data are even more convincing if the salmeterol-fluticasone combination arm is compared with placebo after 3 years of treatment (see below). The data from the TORCH study suggest that regular pharmacologic therapy for COPD may actually change the natural history of the disease by slowing the progressive decline in the lung function.

Regular treatment with LABA reduces the rate of exacerbations by 22% on average (Man et al 2003; Sin et al 2003) and improves the health status and quality of

life (Man et al 2003; Sin et al 2003). A robust hypothesis is that the improvement in the health status related quality of life, usually assessed by means of the St George Respiratory Questionnaire, is determined by the reduction of breathlessness and the increase in the exercise capacity due to the decrease of dynamic lung hyperinflation after bronchodilatation (Cooper 2006).

### **Small airways in COPD**

Three landmark studies (Hogg et al 1968, 2004; Cosio et al 1978; Hogg 2004), among others, documented that small airways are the major site of airflow limitation in COPD (Macklem 1998b; Hogg 2004). The pathologic changes in the lungs of patients with COPD show secretions in the bronchial lumen, inflammatory infiltrate in the bronchial wall, and loss of alveolar attachments (Barnes 2004). These pathologic modifications are mainly located in the small airways. The airway smooth muscle layer, which is the target of the bronchodilating agents, is neither hypertrophic nor hyperplastic. In the small airways, the bronchial wall is thick. These changes are very different in asthma, where the smooth muscle layer in the small airways is much thicker than normal. The contraction of the smooth muscle in the inflammatory environment of the bronchial wall is the mechanism causing airflow obstruction in asthma. By contrast, the airflow limitation in COPD does not seem to be particularly related to the action of the contractile machinery but rather to the loss of lung elastic recoil, to the destruction of the alveolar attachments, and to the dynamic compression of the small airways during expiration (Hogg 2004). However, the significant and persistent, though apparently small, improvement in the FEV<sub>1</sub> reported by all the clinical trials (Man et al 2003; Sin et al 2003) indicates that part of the impediment to expiration is determined by bronchial smooth muscle contraction, and that it is removed by the smooth muscle relaxing agents such as LABAs.

Airway smooth muscle relaxation through  $\beta_2$ -adrenoceptor stimulation, leading to an increase in cyclic adenosine mono-phosphate, improves airway patency and provides also a significant relief from exercise dyspnea (Rennard and Calverley 2006). Interestingly, the improvement in the exercise capacity of COPD patients was not found to be related to changes in FEV<sub>1</sub> but to an increase in the inspiratory capacity (IC), mirroring a decrease in the functional residual capacity (FRC) (Cooper 2006). These results provide an insight into the mechanism through which LABAs relieve dyspnea.

## Pulmonary hyperinflation

Although it was known for many years that retarded expiration due to increased airway resistance and airflow limitation causes an increase in FRC (Macklem 1998a), the key role of pulmonary hyperinflation in the pathophysiology of COPD was brought to the attention of clinical practice more recently (Rossi et al 1991; Cooper 2006). This issue is discussed extensively elsewhere (Calverley and Koulouris 2005). Briefly, increased airway resistance and expiratory airflow limitation retard the rate of expiratory flow such that the tidal expiration is not completed to the relaxed FRC because of the excessive time needed and the new inspiratory effort ensues. Under those circumstances, tidal FRC remains above the relaxed FRC and dynamic hyperinflation occurs because of the discrepancy between the time needed to fully decompress the lungs and the time actually available between two next inspiratory efforts.

The smooth muscle relaxing agents, as LABAs, improve the small airway patency and hence the rate of lung emptying such that following bronchodilatation, dynamic FRC is set at a lower lung volume than the pre-bronchodilatation condition. Breathing at a lower FRC decreases the work of breathing while placing the respiratory muscle in a more favorable geometric arrangement for their pressure generating capacity (Man et al 2004; Gayan-Ramirez et al 2006). The association of the decrease in the work of breathing with a better ventilatory pump performance determines the improvement in exercise tolerance and the reduction of dyspnea.

Only a few papers have addressed the effect of LABAs on pulmonary hyperinflation (Di Marco et al 2003; O'Donnell et al 2004). However, the data are consistent for both salmeterol and formoterol (Di Marco et al 2003; O'Donnell et al 2004). It has been shown that the "small" bronchodilatation is associated with a significant reduction of FRC with a mirror increase in IC. The latter is inversely correlated with dyspnea (assessed by means of the Visual Analog Scale [VAS], the Borg scale or the Baseline [BDI] and Transition [TDI] Dyspnoea Indexes) and it is positively correlated with exercise capacity (Cooper 2006). IC provides the inspiratory reserve when minute ventilation increases to meet the greater metabolic demand during exercise. Therefore, a larger IC allows a greater exercise capacity (Diaz et al 2000; O'Donnell et al 2001). Furthermore, the decrease in FRC increases the distance between tidal breathing and the total lung capacity (TLC). The upper limit for ventilation is reached when about 0.5 L divides the end-inspiratory volume from TLC (Diaz et al 2000; O'Donnell et al 2001).

## LABAs and anticholinergics

Combining  $\beta_2$ -agonists and anticholinergic agents is pharmacologically useful. In fact, the addition of a  $\beta_2$ -agonist decreases the release of acetylcholine because of the modulation of cholinergic neurotransmission by prejunctional  $\beta_2$ -adrenoceptors and, consequently, amplifies the bronchial smooth muscle relaxation directly induced by the anticholinergic agent. Alternatively, the addition of an anticholinergic agent can reduce the peripheral bronchoconstrictor effects of acetylcholine, whose release has been slowed by the  $\beta_2$ -agonist, and in this manner it can amplify the bronchodilation elicited by the  $\beta_2$ -agonist through the direct stimulation of smooth muscle  $\beta_2$ -adrenoceptors (Cazzola and Matera 2006).

Some studies on the acute effect of LABAs in association with tiotropium have shown that the combination of the two drugs generates a greater bronchodilatation than either alone (Cazzola and Matera 2006). One recent prospective, randomized clinical trial addressed the issue of combined therapy in patients with moderate-to-severe COPD. Patients were randomly divided into 3 arms of treatment and followed for 1 year. One-third of patients received tiotropium plus placebo, one-third received tiotropium plus LABA (salmeterol), and one-third received tiotropium plus the salmeterol-fluticasone fixed combination (SFC). The addition of salmeterol to tiotropium did not significantly improve the predetermined outcomes. By contrast, the addition of SFC to tiotropium significantly improved lung function, with an increase in FEV<sub>1</sub> of 110 mL on average, and on health status related quality of life. The addition of either salmeterol or SFC to tiotropium failed to show any effect on the rate of exacerbations, but the addition of SFC to tiotropium reduced the number of hospitalizations. Another recent study in severe-to-very severe COPD has observed that improvement in pulmonary function, expressed as a change in FEV<sub>1</sub>, did not differ between tiotropium and SFC, but the simultaneous administration of the two treatments provided greater improvements in FEV<sub>1</sub> compared with the other two therapeutic regimens taken separately (Cazzola et al 2007a). This is an intriguing result, but the study does not allow to establish if the improvement in lung function caused by combining SFC and tiotropium was linked to the effect of the combination of two long-acting bronchodilators or due to a synergistic interaction between the inhaled corticosteroid and the long-acting bronchodilators, with the resulting synergetic effect being greater than the sum of responses achieved from each drug alone. Interestingly, a recent study has documented that the addition of theophylline on a combination of formoterol and tiotropium in stable COPD did not induce a significant further

improvement in lung function and dyspnea, although 5 out of 18 patients reported an important relief in dyspnea during the theophylline administration period. This finding questions the importance of adding theophylline in stable COPD patients already treated with two long-acting bronchodilators, but also indicates the possibility that some of them can benefit from theophylline because of a symptomatic improvement (Cazzola and Matera 2007).

## LABAs in COPD guidelines

National and international guidelines (British Thoracic Society 2004; Celli and MacNee 2004; Rabe et al 2007) suggest that long-acting bronchodilator therapy should always be considered when patients with COPD are symptomatic, but no distinction is made as to which class of drug should be considered first, although  $\beta_2$ -agonists and anticholinergics are distinct classes of drugs with different mechanisms of action. This is the likely reason for which Tennant et al (2003) suggest that individual COPD patients may respond better to either tiotropium or salmeterol and that an acute bronchodilator test might help to choose the appropriate therapy. However, it has been documented that the bronchodilator effects of tiotropium and salmeterol, evaluated as mean changes from baseline FEV<sub>1</sub>, are similar in patients with stable COPD during the first 3 hours after their acute administration, and consequently the choice of prescribing a long-term therapy with a long-acting bronchodilator should not depend on the simple test of reversibility (Matera et al 2005). In any case, the GOLD treatment recommendations for patients with stable COPD are characterized by a stepwise increase in therapy according to disease severity (Rabe et al 2007). Table 1 illustrates two possible pathways for the regular use of inhaled therapies with increasing COPD severity. The first column represents an evidence-based rationale for the utilization of inhaled therapies in COPD according to the GOLD executive document, while the second column shows the ACP recommendation (Qaseem et al 2007), which considers only the treatment of symptomatic patients. Historically, severity of COPD has been classified according to FEV<sub>1</sub>, but FEV<sub>1</sub> may not correlate directly with symptoms and, consequently a symptomatic approach to therapy using clinical stages may be more useful. Consequently, the ATS/ERS COPD guidelines (Celli and MacNee 2004) have indicated the importance of starting regular maintenance therapy based on the presence of persistent symptoms, regardless of the disease stage. The choice of agents may be based primarily on individual response, cost, side-effect profile and availability.

Nonetheless, Cooper and Tashkin (2005) have described a more explicit and practical patient oriented approach to the hierarchical implementation of pharmacotherapy in COPD. They have proposed a clinical treatment algorithm based on the clinical stage of disease regardless of disease stage or lung function. For patients with intermittent symptoms, as-needed use of a short-acting bronchodilator (eg, ipratropium, salbutamol or both) is recommended. For patients with persistent symptoms, maintenance treatment should be initiated with a long-acting bronchodilator, preferably tiotropium added to salbutamol (suitable alternatives are salmeterol or formoterol added to salbutamol and/or ipratropium, or both); salbutamol should be continued as needed for rescue from symptoms. The final treatment step for patients with frequent exacerbations or inadequate control of symptoms, despite optimal bronchodilator therapy, is a LABA in combination with a long-acting anticholinergic agent, with or without the addition of inhaled corticosteroids.

## Adverse effects of LABA

A recent meta-analysis concluded that treatment with LABAs could be associated with worsening of disease control (Salpeter et al 2006b). Salpeter and colleagues (2004) found that the use of LABA, in COPD patients, did not affect severe exacerbations, but resulted in a significant increase of respiratory deaths compared with placebo. The addition of LABAs to anticholinergics did not improve any clinical outcome in that meta-analysis.

The conclusion on the dangerous consequence of regular treatment with salmeterol in patients with COPD was not confirmed and was opposed, to some extent, by the results of other studies in which LABAs were compared with placebo, inhaled corticosteroids (ICS), both fluticasone (Calverley et al 2003b) and budesonide (Centanni and Di Marco 2005; Cazzola and Hanania 2006), and the combination of salmeterol-fluticasone and formoterol-budesonide (Calverley et al 2003a; Szafranski et al 2003; Cazzola and Dahl 2004). The three prospective, randomized trials (Calverley et al 2003a, b; Szafranski et al 2003) showed a beneficial effect of salmeterol or formoterol compared to placebo and an additional beneficial effect of the ICS-LABA combination compared to both placebo or LABA alone for any of the considered outcomes. Lung function and quality of life were better and the rate of exacerbations was reduced (Man et al 2003; Sin et al 2003).

These results are in line with a more recent three-year large prospective randomized trial (over 6000 COPD patients), ie, the TORCH study (The TORCH Study Group

**Table I** Pharmacological treatment of stable COPD

GOLD stage	GOLD key-points	ACP recommendations
FEV <sub>1</sub> /FVC < 0.70 FEV <sub>1</sub> ≥ 80% pred (I)	Short-acting bronchodilators as needed	
FEV <sub>1</sub> /FVC < 0.70 50% ≤ FEV <sub>1</sub> < 80% pred (II)	Long-acting bronchodilators + Short-acting bronchodilators as needed	
FEV <sub>1</sub> /FVC < 0.70 30% ≤ FEV <sub>1</sub> < 50% pred (III)	Combination of long-acting bronchodilators + Short-acting bronchodilators as needed <sup>b</sup>	Long-acting bronchodilators or Inhaled corticosteroids or Combination inhaled therapies <sup>c</sup>
FEV <sub>1</sub> /FVC < 0.70 FEV <sub>1</sub> < 30% pred or FEV <sub>1</sub> < 50% pred plus chronic respiratory failure <sup>a</sup> (IV)	Combination of long-acting bronchodilators + Inhaled corticosteroids	

<sup>a</sup>Respiratory failure: arterial partial pressure of oxygen (PaO<sub>2</sub>) < 8.0 kPa (60 mmHg) with or without arterial partial pressure of CO<sub>2</sub> (PaCO<sub>2</sub>) > 6.7 kPa (50 mmHg) while breathing air at sea level.

<sup>b</sup>Inhaled corticosteroids are indicated in case of repeated exacerbations requiring treatment with antibiotics or oral glucocorticoids or if positive response (decreased symptoms, increased lung function, and/or reduced health-care utilization).

<sup>c</sup>For symptomatic patients with COPD and FEV<sub>1</sub> < 60% predicted (Qaseem et al 2007).

**Abbreviation:** ACP, American College of Physicians.

2004; Calverley et al 2007), in which the effects of salmeterol for all the considered variables were compared with the placebo and the SFC arms. After 3 years of treatment, the group of patients treated with salmeterol had a significantly better lung function and health related quality of life than the placebo group. The COPD patients treated with the SFC exhibited even better results than both single components and placebo. Furthermore, the mortality for all causes and for respiratory causes in the salmeterol arm was lower, though not significantly, than in the placebo arm. This large 3-year trial, therefore, in line with the previously mentioned shorter clinical trials, does not support the conclusion of the meta-analysis undertaken by Salpeter et al (2006b) whereas it supports the regular use of a LABA in COPD patients. The TORCH study, similarly to the previous clinical trial on salmeterol and SFC, did not report any adverse event related to the treatment with the LABA. In particular, no increase in the rate of death was observed. Also the prospective one-year study in which salmeterol or SFC were added randomly to tiotropium failed to show any adverse effect related to the use of the LABA (Aaron et al 2007).

## LABAs and cardiovascular effects

A recent meta-analysis addressed the issue of cardiovascular effects of  $\beta$ -agonists in patients with obstructive airway diseases, ie, asthma and COPD (Salpeter et al 2006a), and found that initiation of  $\beta_2$ -agonists therapy was associated with significant increase in heart rate and reductions in potassium concentrations. With continuous treatment, the rate of cardiovascular events was increased compared to placebo.

The authors concluded that regular treatment with  $\beta_2$ -agonists could precipitate arrhythmias, ischemia, and congestive heart failure through the activation of  $\beta$ -adrenergic stimulation (Salpeter et al 2004; Salpeter et al 2006a). Clearly, the meta-analysis has severe limitations and the conclusion cannot be taken as definitive. In fact there is a marked heterogeneity among trials in terms of length, selected population, number of patients and documentations of adverse events.

It is well known that LABAs may cause adverse cardiovascular effects (Salpeter et al 2004; Cazzola et al 2005; Salpeter et al 2006b).  $\beta$ -agonists cause palpitation, hypokalemia, and occasionally ventricular arrhythmias (Cazzola et al 2005). These effects are due to systemic absorption of the drug as a result of both the lung deposition and the swallowed portion.

LABAs are selective  $\beta_2$ -adrenoceptor agonists.  $\beta_1$ - and  $\beta_2$ -adrenoceptors coexist in the heart, though  $\beta_1$ -adrenoceptor density is 3-fold higher than that of  $\beta_2$ -adrenoceptors. The presence of  $\beta_2$ -adrenoceptors in the heart explains why  $\beta_2$ -agonists can induce a number of adverse effects that potentially impact on cardiac function. These effects are usually considered to be mild. In any case, it has been shown that full  $\beta_2$ -agonists would elicit a greater response than partial agonists (Hanania et al 2002).

Salmeterol and formoterol have similar effects. However, in patients suffering from COPD with pre-existing cardiac arrhythmias and hypoxemia, the cardiac effects of formoterol 24  $\mu$ g bid are more marked (Cazzola et al 1998). Cazzola et al (1998) concluded that 50  $\mu$ g bid of salmeterol and 12  $\mu$ g bid of formoterol have a reasonable safe margin in this type of

COPD patients. Nonetheless, other authors failed to show any significant difference on the electrocardiogram between placebo and salmeterol (Reisner et al 2003). Heart disease is not currently regarded as a contraindication to cautious use of  $\beta_2$ -agonists in COPD patients (Rennard and Calverley 2006).

Some reports suggest the presence of an association between  $\beta_2$ -agonists and the risk of chronic heart failure. The sympathetic nervous system and pro-inflammatory cytokines are believed to play a key-role in the pathophysiology of congestive heart failure and chronic  $\beta$ -adrenergic stimulation has shown to induce myocardial pro-inflammatory cytokine expression (Murray et al 2000). However, Ng et al (2002) found that a long-term inhaled salmeterol therapy (100  $\mu$ g twice daily) improved pulmonary function, without augmentation of neurohormonal systems or ventricular ectopy, in symptomatic heart failure patients with a left ventricular ejection fraction of less than 40%.

It must be highlighted, in any case, that COPD patients are at increased risk of cardiovascular complications. This might be due to the effects of the smoking practice which affects both the cardiovascular and the respiratory system. On the other hand, COPD amplifies the impact of  $\beta_2$ -agonist on the heart. In patients with COPD, the activity of the cardiac sympathetic nerves may be affected by recurrent hypoxemia, hypercapnia, changes in airway tone, increased intrathoracic pressure as a result of airway obstruction, and large fluctuations in heart rate and blood pressure due to increased respiratory effort (Zimmer et al 2000). Patients with hypoxemic COPD, in particular, have been reported to have subclinical autonomic neuropathy associated with a prolonged QTc interval and an associated risk of ventricular arrhythmias (Stewart et al 1995). The existence of left ventricle myocardial sympathetic nervous alterations as a result of generalised sympathetic autonomic nervous system over activity has been suggested (Sakamaki et al 1999).

### Impact of LABAs on blood gases

It is known that the administration of  $\beta$ -adrenergic agents to patients with airways obstruction often results in a transient decrease in partial pressure of oxygen in arterial blood ( $\text{PaO}_2$ ) despite concomitant bronchodilation (Cazzola et al 2006). The clinical relevance of changes in oxygenation may be considerable for patients with COPD because findings reflecting bronchodilation do not necessarily correlate with the perception of breathlessness, but, apparently, both formoterol and salmeterol result in significant improvement in lung function and significant but small decreases in  $\text{PaO}_2$  and increases in  $\text{P(A-a)O}_2$  (Santus et al 2007). In any case, the

average changes are quite small and of questionable clinical significance. The transient decrease in  $\text{PaO}_2$  with  $\beta$ -adrenergic agents has been attributed to the pulmonary vasodilator action of these agents due to the activation of  $\beta$ -adrenoceptors that are present in pulmonary vessels (Cazzola et al 2007b), increasing blood flow to poorly ventilated lung regions and thus increasing ventilation-perfusion (VA/Q) inequality, inducing a shunt-like effect (Wagner et al 1978).

### Conclusions

Long-acting bronchodilators are the first-line treatment of symptomatic (poor exercise tolerance) patients with COPD. In this class of drugs, LABAs (salmeterol and formoterol) have a key-role in the pharmacologic therapy of COPD. LABAs improve lung function and health status related quality of life, and reduce the rate of exacerbations. These effects can be enhanced by the combination of LABAs with tiotropium, and with inhaled corticosteroids. An additional benefit can be reached by combining the three drugs in the treatment. LABAs may have adverse cardiovascular effects, which are amplified in COPD patients with concomitant cardiac disorders. In these patients, LABAs should be used with some cautions. At the present level of our knowledge, the use of LABAs in COPD patients, even patients with cardiac disease comorbidity, does not put "caveats" similar to the use of LABAs in asthma. This might be considered to some extent surprising, because COPD patients are older than patients with asthma and have a larger comorbidity for cardiac disorders. COPD patients with cardiac comorbidity may be treated with both  $\beta$ -blockers and  $\beta$ -agonists at the same time.

The important message from many recent and large clinical trials is that COPD patients should be treated with inhalation drugs. LABAs, tiotropium, and LABA plus ICS combinations are available and can be used either separately or in association. Patients taking regular bronchodilating therapy have a better quality of life than patients who do not take regular bronchodilating medications. The potential adverse cardiovascular effects of LABAs and the presence of cardiac comorbidity in COPD patients suggest caution but do not represent a contraindication.

### Disclosures

None of the authors has any conflicts of interest to declare.

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