

β -AGONISTS, β -BLOCKERS AND OBSTRUCTIVE AIRWAY DISEASE

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Primum non nocere, or "First, do no harm". This is one of the most basic and repeated quotations in medical lore, attributed to Hippocrates. It reminds a physician that he or she must consider the possible harm that any intervention might do. However, in clinical practice, this is not an easy task.

β 2-agonist use in patients with obstructive airway disease has been associated with an increased risk for myocardial infarction, congestive heart failure, cardiac arrest and acute cardiac death.

On the other side, β -blockers are known to reduce morbidity and mortality in patients with cardiac disease, but have been associated with acute exacerbations of bronchospasm and death when they are used in patients with asthma and COPD.

In this issue, we tried to find data from published articles that could give us some answers to the following questions:

1. Are β -agonists harmful for heart?
2. Are β -blockers harmful for lung?
3. Can they be used together?

β -adrenergic receptors have been classified into at least 3 groups. β 1 and β 2 receptors coexist in the heart, generally in a ratio 3:1, respectively (1,2). β 2 receptors are also present on adrenergic terminals in the heart, where they facilitate norepinephrine release. β 2 receptors are found predominantly in bronchial and vascular smooth muscle, peripheral leucocytes and adrenergic nerves. β 3 are found mainly on adipose tissue. With less importance, β 3 also exists in the heart (3).

Sympathetic nervous system is an important regulator of myocardial performance.

Norepinephrine and epinephrine affect the activity and function of cardiac myocytes mainly through the stimulation of β -adrenergic receptors. After neuro-

transmitter activation β -receptors stimulate adenylyl cyclase; the interaction between the receptor and the enzyme is not direct but is mediated by a G protein that is called Gs. Stimulation of adenylyl cyclase leads to the accumulation of cyclic AMP that, beyond other effects, modulates calcium entrance into cardiac myocytes and consequent muscular contraction (4).

Positive inotropic and chronotropic responses are mainly mediated by β 1-receptor stimulation. Increases in heart rate and myocardial oxygen demand can lead to ischemia and cardiac myocyte necrosis, progression of congestive heart failure, or sudden death.

β 2 stimulation is also associated to cardiac myocyte growth (6,7) and direct myocardial injury (8-10). Myocyte toxicity, together with prolonged corrected Q-T interval and hypokalemia that are also a consequence of β 2 stimulation in the heart and skeletal muscle, are associated with ventricular and atrial arrhythmias.

β -blocking has opposite effects and is associated to negative inotropic and chronotropic responses, reduces myocyte toxicity and apoptosis and has anti-arrhythmic effects (10,11).

The use of β -adrenergic blocking agents reduces morbidity and mortality in patients with ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, hypertension and also reduces perioperative complications.

There are about 10-12 β -blocking drugs that we use in clinical practice. Beyond their common effects, they have very different pharmacological characteristics that assume clinical relevance:

- Relative selectivity for β 1 and β 2 receptors (12).
- Intrinsic Sympathomimetic Activity (I.S.A.)- partial agonist activity.
- Differences in lipid solubility, and general pharmacokinetic properties.

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- Effects that are not dependent of β receptor blocking: vasodilator effect (blockade of β -adrenergic receptors), citoprotector and specific antioxidant effects (13,14).

β 2-agonists exert physiologic effects that are opposite to β -blockers and may be expected to have deleterious cardiovascular effects.

β 2-stimulation has a bronchodilator effect and the regular use of β 2 agonists became a standard of care for the management of reactive airway disease, since the 1960s, without good scientific data concerning long term efficacy and safety. In fact, to date no randomized trials have demonstrated a reduction in disease progression or in mortality, with the use of β 2 agonists.

Despite the lack of data, present guidelines recommend intermittent use of short-acting β 2-agonists as rescue treatment for exacerbations and regular use of long-acting β 2-agonists as second line treatment to be added to corticosteroids

Case-control studies have found an association between β 2 agonist use and an increase in cardiovascular morbidity and mortality. β 2-agonists have been associated with an increased risk for fatal and non fatal myocardial infarction, with higher risks seen for those with a history of cardiovascular disease and for new users of β 2-agonists (16,17). β -agonist use also has been associated with an increased risk for heart failure and cardiomyopathy, cardiac arrest and acute cardiac death, with higher risks associated with nebulized and oral treatment compared to metered-dose inhaler treatment (18-22).

To assess the cardiovascular safety of β 2 agonist use in patients with obstructive airway disease, defined as asthma or COPD, a recent meta-analysis, collating evidence from 33 randomized, placebo-controlled trials of β 2 agonist treatment, evaluated the short term effect on heart rate and potassium concentrations, and long-term effects on adverse cardiovascular events (23).

13 trials studied single dose treatment in a total of 232 patients. 20 trials involved 6623 patients who received continued treatment (3 days to 1 year).

The main results of the meta-analysis are as follows: A single dose of a β 2 agonist caused significant increases in heart rate and reductions in potassium concentrations, compared to placebo.

In the longer duration trials, treatment with a β -agonist was associated with a highly significant increased

risk for adverse cardiovascular events ($p=0,00001$). The majority of events recorded were due to sinus tachycardia (minor event). The major adverse events recorded included ventricular tachycardia, atrial fibrillation, syncope, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death. The relative risk (RR) for major events did not reach statistical significance.

Sinus tachycardia is a marker of sympathetic stimulation, which in itself is associated with a poor cardiovascular prognosis and also directly contributes to cardiac work and strain. Elevated heart rate has been shown to be a strong independent risk factor for development of coronary artery disease, fatal myocardial infarction, sudden death, cardiovascular mortality, and total mortality (24-30).

Hypokalemia occurs with β 2 stimulation as a result of intracellular shifts of potassium into skeletal muscle and has been associated with an increased risk for ventricular tachycardia and fibrillation in susceptible patients (31). In patients with obstructive airway disease, the levels of serum potassium may be decreased further with the use of corticosteroids and diuretics, and the cardiac effects of hypokalemia can be aggravated by underlying hypoxemia (32,33).

This analysis reinforces the accumulating evidence that β 2-agonists, when administered regularly, may increase the risk for adverse cardiovascular events, compared to placebo.

There is no doubt about the major beneficial impact of β -blockers on the management of several cardiovascular diseases. They have an established role in cardioprotection both in primary and secondary prevention (34,35).

Many patients with reactive airway disease, have concomitant conditions such myocardial infarction or cardiac arrhythmias which necessitate the use of β -blocker.

Yet, physicians have persistently resisted the use of β -blockers in patients with acute or chronic obstructive lung disease, and many people who might otherwise have survived as a result of β -blocker use have probably died because they were not given these agents (35-38).

The reason for this paradox is that a number of publications have implicated β -blockers as the causative agent in fatal exacerbations of bronchospasm. Dramatic descriptions of death and disaster have mostly appeared as case reports and have largely involved noncardioselective β -blockers that are much

more likely than cardioselective agents to affect bronchial tone (39-42).

Cardioselective β -blockers, or β_1 -blockers such as atenolol, bisoprolol and metoprolol, have greater than 20 times more affinity for β_1 -receptors than for β_2 -receptors and in theory should pose much less risk for bronchoconstriction and at therapeutic doses, their β_2 -blocking effect is negligible.

Several studies have evaluated the differential effects of a cardioselective and noncardioselective β -adrenergic blocker on parameters of pulmonary function in patients with asthma or COPD, with or without cardiovascular diseases.

■ **The ACC/AHA guidelines recommend the following:**

"Although relative contraindications once may have been thought to preclude the use of β -blockers in some patients, new evidence suggests that the benefits of β -blockers in reducing reinfarctions and mortality may actually outweigh its risks, even in patients with asthma; insulin-dependent diabetes mellitus; chronic obstructive pulmonary disease; severe peripheral vascular disease, PR interval $>0,24$ s; and moderate LV failure. It is also emphasized that the use of β -blockers in such patients requires careful monitoring of the patient to be certain that adverse events do not occur" (43).

Salpeter and associates analysed data from randomized, blinded, placebo-controlled trials, to evaluate the effects of cardioselective β -blockers on patients with mild to moderate reactive airway disease (asthma or COPD with reversible component)(44).

Of the 29 studies included in this meta-analysis, 19 studied single dose treatment in a total of 240 patients. 10 studies involved 141 participants who received continued treatment (3 days to 4 weeks).

β -blockers without I.S.A. that were used included atenolol, metoprolol, bisoprolol and practolol. Those with I.S.A. included celiprolol, acebutolol and xamoterol.

Compared to placebo, single doses of cardioselective β -blocker as a group were associated with a 7,46% reduction in forced expiratory volume in one second (FEV1) but with a 4,63% increase in FEV1 after β -agonist was given. None of the studies demonstrated increased respiratory symptoms among patients.

On subgroup analysis β_1 -blockers without I.S.A. were associated with a 6,5% reduction in FEV1 compared to those with I.S.A. However, treatment with β_1 -blockers without I.S.A. was associated with a 9,7% increase in FEV1 in response to β -agonist.

In the continued treatment trials, cardioselective β -blockers as a group did not significantly differ from placebo in terms of FEV1 response and number of patients with symptoms. Cardioselective β -blockers produced an increase in FEV1 compared with placebo after β -agonist was given.

On subgroup analysis, no significant difference in FEV1 response was observed for β_1 -blockers without I.S.A. compared to those with I.S.A. However, β -blockers without I.S.A. produced a 12,6% increase in FEV1 after β -agonist administration compared to β -blockers with I.S.A.

These results indicate that for cardioselective β -blockers without intrinsic sympathomimetic activity, the small drop in FEV1 noted with a single dose is attenuated over a few days to weeks. In addition, FEV1 increases in response to β_2 -agonist administration compared with placebo, and this increase is maintained with continued treatment.

The competing risks and benefits of β_2 -agonist use has been topic of much discussion. β_2 -agonists have been the mainstay of therapy for obstructive lung diseases over the past 50 years, with studies demonstrating sustained improvements in peak flows and respiratory symptoms. However evidence also have been accumulating that β_2 -agonist use is associated with an increase in morbidity and mortality.

Although originally most of the deaths were thought to be due to cardiac events, more recently, evidence has been indicating that the regular administration of β_2 -agonists may result in tolerance (tachyphylaxis) to their effects and this may also contribute to an increased risk for fatal and near fatal asthma attacks (45).

The β -adrenergic system has a very sensitive negative feedback mechanism as an adaptative response to either stimulation or blockade of the receptors.

Overstimulation by beta-mimetic drugs results in loss of β -adrenergic receptor activity (Desensitization or tachyphylaxis). It generally evolves in two steps: loss of their function (uncoupling between the receptors-Gs proteins and adenylyl cyclase) followed by a decrease of their number (downregulation) (46,47). This tolerance to adrenergic stimulation could explain why the highest risk for adverse cardiovascular events is seen during the initiation of β_2 -agonist therapy.

Conversly, β -blockade results in increased efficiency of coupling between receptors-Gs proteins and adenylyl cyclase, and increased number of receptors (upregulation) (48,49).

FEV1 increases in response to β_2 -agonist administration on patients taking cardioselective β -blockers, could be explained by upregulation or sensitization of β_2 -receptors that is accompanied by an increase effect of endogenous and exogenous β_2 -agonist stimulation.

Another meta-analysis was performed to assess the effects of cardioselective β -blockers in patients with COPD. Data were collected from randomized, blinded, controlled trials of single dose or longer duration studies (50).

Cardioselective β -blockers produced no statistically significant change in FEV1 or respiratory symptoms compared to placebo, given as a single dose or in continued use.

The cumulative evidence from these meta-analysis provides substantial assurance to give the following answers:

- β_2 -agonists, when administered regularly, may increase the risk of cardiovascular events.
- Cardioselective β -blockers are safe and should be considered in patients with mild to moderate asthma or patients with COPD. These drugs should be initiated at low doses and if tolerated, the dose should be increased as needed to achieve the desired clinical effect.
- Cardioselective β -blockers may actually be beneficial when used together with β_2 -agonists by enhancing sensitivity to β -adrenergic stimulation.

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