Cardiovascular Effects of β-Agonists in Patients With Asthma and COPD: A Meta-Analysis
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Background: β-Adrenergic agonists exert physiologic effects that are the opposite of those of β-blockers. β-Blockers are known to reduce morbidity and mortality in patients with cardiac disease. β2-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.

Objectives: To assess the cardiovascular safety of β2-agonist use in patients with obstructive airway disease, defined as asthma or COPD.

Methods: A meta-analysis of randomized placebo-controlled trials of β2-agonist treatment in patients with obstructive airway disease was performed, to evaluate the short-term effect on heart rate and potassium concentrations, and the long-term effect on adverse cardiovascular events. Longer duration trials were included in the analysis if they reported at least one adverse event. Adverse events included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, or sudden death.

Results: Thirteen single-dose trials and 20 longer duration trials were included in the study. A single dose of β2-agonist increased the heart rate by 9.12 beats/min (95% confidence interval [CI], 5.32 to 12.92) and reduced the potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54), compared to placebo. For trials lasting from 3 days to 1 year, β2-agonist treatment significantly increased the risk for a cardiovascular event (relative risk [RR], 2.54; 95% CI, 1.59 to 4.05) compared to placebo. The RR for sinus tachycardia alone was 3.06 (95% CI, 1.70 to 5.50), and for all other events it was 1.66 (95% CI, 0.76 to 3.6).

Conclusion: β2-Agonist use in patients with obstructive airway disease increases the risk for adverse cardiovascular events. The initiation of treatment increases heart rate and reduces potassium concentrations compared to placebo. It could be through these mechanisms, and other effects of β-adrenergic stimulation, that β2-agonists may precipitate ischemia, congestive heart failure, arrhythmias, and sudden death.

Key words: adrenergic β-agonists; adverse effects; asthma; cardiovascular; COPD

Abbreviations: CI = confidence interval; OR = odds ratio; RR = relative risk

The β-adrenergic system contains β1 and β2 receptors that are found in varying concentrations in the heart and lung, as well as in peripheral tissues throughout the body.1,2 β1-Adrenergic receptors and β2-adrenergic receptors coexist in the heart, generally in a ratio of 3:1, respectively.3 β2 Receptors are also present on adrenergic nerve terminals in the heart, where they facilitate norepinephrine release.1

The stimulation of either receptor results in positive inotropic and chronotropic responses, cardiac myo-
cyte growth, and cardiac toxicity. $^{1}$ $\beta_2$ Receptors are found predominately in bronchial and vascular smooth muscle, peripheral leukocytes, and adrenergic nerves. $^{2}$ $\beta_2$-Agonists, such as albuterol and salmeterol, are widely used as bronchodilators in the treatment of asthma and COPD.

The use of $\beta$-blockers has been shown to reduce morbidity and mortality in patients with ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, and hypertension, as well as in the perioperative period. $^{1,3-7}$ $\beta$-Agonists exert physiologic effects that are the opposite of those of $\beta$-blockers and may be expected to have deleterious cardiovascular effects. $^{8}$ Doubts have gradually been emerging concerning the cardiovascular safety of $\beta_2$-agonist use, especially in patients who are at risk for heart disease. $^{2,9}$ Case-control studies $^{10-16}$ have demonstrated an association between $\beta_2$-agonist use and an increased risk for myocardial infarction, congestive heart failure, cardiac arrest, and acute cardiac death, with odds ratios (ORs) ranging from 1.3 to 3.4.

The objective of this analysis was to evaluate the cardiovascular effects of $\beta_2$-agonist use in patients with obstructive airway disease, which was defined as asthma or COPD. Data from randomized placebo-controlled trials were pooled in order to assess the short-term effect of $\beta_2$-agonist use on heart rate and potassium concentration, and the long-term effect on adverse cardiovascular events. The results of this meta-analysis also have been reported in a systematic review on the cardiovascular safety of $\beta$-agonist use. $^{17}$

**Materials and Methods**

**Search Strategy**

A comprehensive search of the EMBASE, MEDLINE, and CINAHL databases was performed to identify randomized placebo-controlled trials on $\beta$-agonist use in patients with obstructive airway disease, published between 1966 and June 2003. The search was performed using the terms bronchodilator, sympathomimetic, adrenergic $\beta$-agonist, albuterol, salbutamol, bitolterol, isoetharine, metaproterenol, salmeterol, terbutaline, fenoterol, formoterol, procaterol, isoproterenol, reproterol, efor- moterol, or bambuterol, and asthma, $^{*}$ bronchial hyperreactivity, respiratory sounds, wheezing, $^{*}$ respiratory hypersensitivity, obstructive lung disease, obstructive airway disease, obstructive pulmonary disease, or COPD. Trials were not excluded on the basis of language. The search was further augmented by scanning references of identified articles and reviews.

**Study Selection**

Two investigators independently evaluated studies for inclusion. The observed percentage agreement between raters for the assessment of inclusion was calculated using the $k$-statistic. $^{18}$ Trials were considered if they were randomized, placebo-controlled trials of $\beta_2$-agonist use in patients with asthma or COPD.

Single-dose trials were included if they provided extractable data on heart rate or potassium concentrations. Heart rates in the trials were recorded at rest, with measurements made manually, from an ECG, or as a mean value from a cardiac monitor. Longer duration trials were included if they reported at least one adverse cardiovascular event, which was defined as sinus or ventricular tachycardia, atrial fibrillation, syncope, myocardial infarction, congestive heart failure, cardiac arrest, or sudden death. Trials were included even if they allowed for open-label “rescue” $\beta_2$-agonist use in both the treatment and placebo groups.

**Assessment of Validity**

The methodological quality of each included trial was assessed. $^{19}$ A score of A, B, or C was given to trials using the following factors: (1) Was the trial randomized, and if so, was the randomization procedure adequate? (2) Were the patients and people administering the treatment blind to the intervention? (3) Did trials utilize a crossover design or were parallel groups studied? Two reviewers independently assessed quality scores, and interrater agreement was calculated using the $k$-statistic.

**Data Extraction and Synthesis**

Two reviewers independently extracted data from the selected articles, reconciling differences by consensus. In addition, attempts were made to contact the investigators to obtain additional information concerning cardiovascular events.

For single-dose studies, the group mean heart rates and potassium concentrations were measured for active treatment and placebo, and the placebo effect was subtracted from the treatment effect. The net treatment effects for each trial then were pooled to obtain a weighted mean difference, using the random-effects model for continuous outcomes. $^{20}$ The random-effects model was used because it accounts for the possibility of significant interstudy heterogeneity. The analyses were performed using a software package (Meta View, version 4.1; Cochrane Library software, Update Software; Oxford, UK). In order to test for interstudy variability, the $\chi^2$ value was calculated for the assumption of homogeneity, with the statistical significance set at $p < 0.1$.

For longer duration trials, the rate of adverse cardiovascular events was measured for therapy with $\beta_2$-agonists and for placebo in each trial, and the relative risk (RR) was calculated as the ratio of the treatment event rate to the placebo event rate. Only trials that reported at least one event could be used in the calculation of RR. Adverse events recorded included sinus and ventricular tachycardia, syncope, atrial fibrillation, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death. It was chosen to include sinus tachycardia because it is an arrhythmia that can herald a poor prognosis when associated with underlying cardiac conditions. $^{21}$ Mild adverse outcomes that were not recorded included palpitations, chest pain, hypertension, and asymptomatic abnormalities found on ECG such as ectopic beats, ischemic changes, or conduction abnormalities.

The RRs for cardiovascular events in each trial were pooled using the fixed-effects model for dichotomous outcomes. $^{22}$ The data were analyzed separately for sinus tachycardia, which was considered to be a minor event, and for all other events, which were considered to be more clinically significant. The fixed-effects model was chosen because minimal heterogeneity was noted in the analysis. The results then were compared to the random-effects model.
Results

Search Results

The electronic database search identified approximately 5,000 articles, and, of these, 185 were randomized, placebo-controlled trials of β2-agonist use in patients with obstructive airway disease. After scanning references from selected articles, an additional six potentially relevant trials were identified. Of these 191 studies, 13 single-dose trials and 20 longer duration trials met the inclusion criteria. The κ-statistic for interrater agreement on study eligibility was 0.98 (95% confidence interval [CI], 0.96 to 1.00). Consensus was reached on the remaining trials. Trials were excluded for the following reasons: 38 single-dose trials did not provide extractable data on heart rate or potassium concentrations; 115 longer duration trials did not report adverse cardiovascular events or did not provide extractable data; and 5 trials provided data on participants who were already included in the analysis.

Trial Characteristics

The characteristics of each study can be found in Table 1. Of the single-dose trials, seven were of asthma, five were on COPD and one reported data on both.23–25 There were a total of 232 participants, with a mean age of 56.6 years. Of the longer duration trials, 14 were of asthma and 6 were of COPD.36–55 There was a total of 6,623 participants with a mean age of 52.2 years in these trials, which ranged in duration from 3 days to 1 year with a mean trial duration of 4.7 months. All but one trial allowed for the use of rescue β2-agonist use in both the treatment and placebo groups.

Methodological Quality of Included Studies

All of the single-dose trials were double-blind or single-blind crossover trials that received a B quality score. Of the longer duration trials, 15 were double-blind, parallel-group studies that received an A quality score, and 5 were single-blind or double-blind crossover trials that received a B score. The κ score for interrater agreement on methodological quality scores was 1.00.

Quantitative Data Synthesis

A single dose of a β2-agonist caused an increase in heart rate of 9.12 beats/min (95% CI, 5.32 to 12.92) compared to placebo (Fig 1). The administration of a single dose also caused a reduction in potassium concentration by 0.36 mmol/L (95% CI, 0.18 to 0.54) compared to placebo (Fig 2).

In the longer duration trials, treatment with a β-agonist was associated with a significantly increased risk for adverse cardiovascular events (RR, 2.54; 95% CI, 1.59 to 4.05) compared to that for placebo (Fig 3). These results were highly significant (p = 0.00001). The random-effects method did not give significantly different results (RR, 2.23; 95% CI, 1.37 to 3.69). The majority of events recorded after β-agonist use were due to sinus tachycardia. The risk for sinus tachycardia was significantly increased (RR, 3.06; 95% CI, 1.7 to 5.5) compared to that when receiving placebo. The major adverse events recorded included ventricular tachycardia, atrial fibrillation, syncope, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death. The RR attributed to these major cardiovascular events was 1.61 (95% CI, 0.76 to 3.42), which did not reach statistical significance.

Interstudy Variability

There was evidence for significant interstudy variance in the analysis of heart rate and potassium concentrations, with p values < 0.001. No evidence of heterogeneity was noted in the analysis of RR, with a p value for heterogeneity of 0.93.

Discussion

In summary, the initiation of β2-agonist therapy was associated with significant increases in heart rate and reductions in potassium concentrations, which are known to be common systemic effects of β-adrenergic stimulation, compared to placebo. With continued treatment, the rate of cardiovascular events was increased compared to placebo, with a significant increase in sinus tachycardia and a nonsignificant trend toward an increase in major cardiovascular events. It is possible that β2-agonists could precipitate arrhythmias, ischemia, and congestive heart failure through the activation of β-adrenergic stimulation.8,56

Case-control studies have found an association between β2-agonist use and an increase in cardiovascular morbidity and mortality. β2-agonists have been associated with an increased risk for fatal and nonfatal myocardial infarction (adjusted OR, 1.67; 95% CI, 1.07 to 2.60), with higher risks seen for those with a history of cardiovascular disease (adjusted OR, 3.22; 95% CI, 1.63 to 6.35) and for new users of β-agonists (adjusted OR, 7.32; 95% CI, 2.34 to 22.8).11 Inhaled β-agonist use also has been associated with an increased risk for heart failure (adjusted OR, 3.41; 95% CI, 1.99 to 5.86) and cardiomyopathy (adjusted OR, 3.2; 95% CI, 1.4 to 7.1), with no difference found between the development of idiopathic or ischemic cardiomyopathy.12,14,15 β-Agonist
<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design/Duration</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Participants, No.</th>
<th>Dropout Rate, %</th>
<th>Age, yr</th>
<th>Active Interventions</th>
<th>Outcomes Measured</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalbers et al36/2002</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: COPD Exclusion: asthma, allergic rhinitis, eosinophilia, recent respiratory tract infection, heart disease, other significant illness</td>
<td>692</td>
<td>17</td>
<td>62</td>
<td>Inhaled formoterol</td>
<td>FEV₁, symptoms rescue β-agonist use</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Anderson et al37/1979</td>
<td>Double-blind, crossover/3 d</td>
<td>Inclusion: asthma Exclusion: none listed</td>
<td>17</td>
<td>0</td>
<td>52</td>
<td>Inhaled fenoterol, terbutaline</td>
<td>Peak expiratory flow, symptoms</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Bennett et al38/1994</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: mild asthma Exclusion: significant other medical problems</td>
<td>12</td>
<td>0</td>
<td>29-54</td>
<td>Inhaled salmeterol, salbutamol</td>
<td>Pulse, potassium* level, FEV₁, BP</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Bensch et al39/2001</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: mild to moderate asthma Exclusion: clinically significant, uncontrolled major organ system dysfunction of respiratory or cardiovascular system</td>
<td>541</td>
<td>15</td>
<td>35</td>
<td>Inhaled formoterol, albuterol</td>
<td>FEV₁, asthma symptoms, rescue β-agonist use</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Boyd40/1995</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: severe, chronic asthma Exclusion: concurrent uncontrolled systemic disease, recent acute respiratory infection</td>
<td>181</td>
<td>34</td>
<td>47</td>
<td>Inhaled salmeterol</td>
<td>Peak expiratory flow, symptoms rescue β-agonist use</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Braden et al41/1998</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: asthma, nonsmoking Exclusion: recent β-agonist use or caffeine-containing beverages</td>
<td>8</td>
<td>0</td>
<td>32</td>
<td>Nebulized terbutaline</td>
<td>Pulse, potassium, M-mode echocardiography</td>
<td></td>
</tr>
<tr>
<td>Braun and Levy42/1991</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: COPD Exclusion: cardiovascular, renal, hepatic, endocrine, metabolic or other systemic disease, urinary retention, prostatic hypertrophy, or glaucoma</td>
<td>72</td>
<td>0</td>
<td>61</td>
<td>Inhaled albuterol</td>
<td>Pulse, BP, FEV₁, FVC</td>
<td>Inhaled ipratropium also studied</td>
</tr>
<tr>
<td>Buch and Bundgaard43/1984</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: asthma, treated with inhaled β-agonists Exclusion: recent exacerbation</td>
<td>8</td>
<td>0</td>
<td>38</td>
<td>Nebulized or IM terbutaline</td>
<td>Pulse, BP, echocardiography</td>
<td></td>
</tr>
<tr>
<td>Burgess et al44/1998</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: mild-to-moderate asthma Exclusion: COPD</td>
<td>20</td>
<td>0</td>
<td>30</td>
<td>Inhaled formoterol</td>
<td>Pulse, potassium level, BP, ECG changes, glucose, FEV₁</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates that the study characteristics are partial or not fully available.
<table>
<thead>
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<th>Outcomes Measured</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgess et al²⁷/1998</td>
<td>Double-blind, crossover/ single-dose</td>
<td>Inclusion: mild asthma Exclusion: regular use of β-agonist</td>
<td>8</td>
<td>0</td>
<td>21-26</td>
<td>Inhaled formoterol under conditions of normoxia and hypoxia</td>
<td>Pulse, potassium, BP</td>
<td>Hypoxia induced by breathing nitrogen/oxygen mixture</td>
</tr>
<tr>
<td>Cazzola et al²⁹/1998</td>
<td>Single-bind, crossover/ single-dose</td>
<td>Inclusion: COPD with preexisting cardiac arrhythmias and hypoxemia Exclusion: corticosteroid use, recent respiratory tract infection, myocardial infarction, decompensated heart failure, unstable angina, or known severe arrhythmia</td>
<td>12</td>
<td>0</td>
<td>60</td>
<td>Inhaled formoterol, salmeterol</td>
<td>Holter monitor, potassium level</td>
<td></td>
</tr>
<tr>
<td>Chan et al³⁰/1988</td>
<td>Double-blind, crossover/ single-dose</td>
<td>Inclusion: stable COPD Exclusion: cardiac disease</td>
<td>10</td>
<td>0</td>
<td>67</td>
<td>Oral terbutaline</td>
<td>Pulse, right and left ventricular ejection fractions, FEV₁, FVC</td>
<td></td>
</tr>
<tr>
<td>Chapman et al⁴⁰/2002</td>
<td>Double-blind, parallel-group/6 mo</td>
<td>Inclusion: COPD Exclusion: respiratory tract infection, recent COPD hospitalization, concurrent respiratory disorders, pregnancy</td>
<td>408</td>
<td>12</td>
<td>Over 40</td>
<td>Inhaled salmeterol</td>
<td>FEV₁, symptoms, rescue β-agonist use</td>
<td>All patients were receiving inhaled anticholinergic therapy; all owed for rescue β-agonist use</td>
</tr>
<tr>
<td>Dahl et al³³/2001</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: COPD Exclusion: asthma, respiratory tract infection, long-term oxygen therapy, corticosteroid use, oral β-agonist use</td>
<td>780</td>
<td>11</td>
<td>64</td>
<td>Inhaled formoterol</td>
<td>FEV₁, symptoms</td>
<td>Inhaled ipratropium also studied; allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Donohue et al³⁴/2002</td>
<td>Double-blind, parallel-group/6 mo</td>
<td>Inclusion: COPD Exclusion: asthma, allergic rhinitis, eosinophilia, recent respiratory tract infection</td>
<td>623</td>
<td>19</td>
<td>65</td>
<td>Inhaled salmeterol</td>
<td>FEV₁, symptoms, rescue β-agonist use</td>
<td>Inhaled tiotropium also studied; allowed for rescue β-agonist use</td>
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<tr>
<td>D’Uzzo et al³⁴/2001</td>
<td>Double-blind, parallel-group/6 mo</td>
<td>Inclusion: asthma Exclusion: uncontrolled pulmonary or systemic disease, psychological conditions</td>
<td>911</td>
<td>22</td>
<td>46</td>
<td>Nebulized salmeterol</td>
<td>Asthma exacerbations</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
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<tr>
<td>Fitzpatrick et al 1990</td>
<td>Double-blind, crossover/2 wk</td>
<td>Inclusion: nocturnal asthma Exclusion: none listed</td>
<td>20</td>
<td>15</td>
<td>39</td>
<td>Inhaled salmeterol, salbutamol</td>
<td>Peak expiratory flow rates, sleep quality</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Hall et al 1994</td>
<td>Single-blind, crossover/single-dose</td>
<td>Inclusion: COPD with severe chronic airflow obstruction Exclusion: theophylline use, history of arrhythmias or heart disease</td>
<td>22</td>
<td>0</td>
<td>67</td>
<td>Nebulized salbutamol</td>
<td>Heart rhythm, potassium level</td>
<td></td>
</tr>
<tr>
<td>Jartti et al 1997</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: children with bronchial asthma Exclusion: diabetes mellitus, cardiovascular, GI, urinary tract, CNS, or peripheral nervous system disease</td>
<td>8</td>
<td>0</td>
<td>11</td>
<td>Inhaled salbutamol</td>
<td>Pulse, heat-to-heat variability of heart rate and BP</td>
<td></td>
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<tr>
<td>Marlin et al 1978</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: asthma or chronic bronchitis Exclusion: none listed</td>
<td>12</td>
<td>0</td>
<td>32-72</td>
<td>Inhaled fenoterol</td>
<td>Pulse, FEV₁</td>
<td>Ipratropium also studied</td>
</tr>
<tr>
<td>Milgrom et al 2001</td>
<td>Double-blind, parallel-group/3 wk</td>
<td>Inclusion: children with asthma Exclusion: allergy to study medications, lower respiratory tract infection, abnormal ECG</td>
<td>335</td>
<td>15</td>
<td>9</td>
<td>Nebulized levallbuterol, racemic albuterol</td>
<td>FEV₁, FVC, symptoms</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Nathan et al 1995</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: asthma Exclusion: smoking history</td>
<td>556</td>
<td>1</td>
<td>12-73</td>
<td>Inhaled salmeterol, albuterol</td>
<td>Adverse events, pulse, BP</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Nielsen et al 1999</td>
<td>Double-blind, parallel-group/2 wk</td>
<td>Inclusion: steroid-dependent asthma Exclusion: stable asthma when corticosteroid tapered off</td>
<td>34</td>
<td>0</td>
<td>44</td>
<td>Inhaled salmeterol</td>
<td>FEV₁, peak expiratory flow, rescue β-agonist use, minimal accepted dose of corticosteroid</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Rennard et al 2001</td>
<td>Double-blind, parallel-group/3 mo</td>
<td>Inclusion: COPD Exclusion: recent pulmonary infection, significant cardiovascular disease, malignancy, abnormal ECG</td>
<td>405</td>
<td>18</td>
<td>64</td>
<td>Inhaled salmeterol</td>
<td>FEV₁, FVC, symptoms, exacerbations, adverse events</td>
<td>Inhaled ipratropium also studied; allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Richter et al 2000</td>
<td>Single-blind, cross-over/1 y</td>
<td>Inclusion: moderate-to-severe asthma Exclusion: significant nonrespiratory illnesses, pregnancy</td>
<td>80</td>
<td>9</td>
<td>48</td>
<td>Inhaled salbutanol, fenoterol</td>
<td>Asthma exacerbations, symptoms, rescue β-agonist use, peak expiratory flow</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
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<tr>
<td>Rossi et al&lt;sup&gt;20&lt;/sup&gt;/2002</td>
<td>Double-blind, parallel-group/1 yr</td>
<td>Inclusion: COPD Exclusion: uncontrolled pulmonary or systemic disease</td>
<td>854</td>
<td>27</td>
<td>63</td>
<td>Inhaled formoterol</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, symptoms, rescue β-agonist use</td>
<td>Oral theophylline also studied; allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Siegel et al&lt;sup&gt;34&lt;/sup&gt;/1985</td>
<td>Double-blind, parallel-group/2 wk</td>
<td>Inclusion: asthma Exclusion: oral corticosteroids, concomitant β-blockers, bronchiectasis, cystic fibrosis, significant concurrent disease, recent oral β-agonists</td>
<td>45</td>
<td>13</td>
<td>18–55</td>
<td>Oral procaterol</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FVC, symptoms</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Spector and Garza Gornez&lt;sup&gt;56&lt;/sup&gt;/1977</td>
<td>Double-blind, crossover/3 d</td>
<td>Inclusion: asthma Exclusion: cardiovascular, hepatic, renal, endocrinologic, or metabolic disease, other than diabetes mellitus</td>
<td>24</td>
<td>33</td>
<td>14–65</td>
<td>Nebulized albuterol, isoproterenol</td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, FVC, pulse</td>
<td>Allowed for rescue β-agonist use</td>
</tr>
<tr>
<td>Vathenen et al&lt;sup&gt;44&lt;/sup&gt;/1988</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: chronic bronchitis with severe airflow limitation Exclusion: use of corticosteroids or nebulized bronchodilator</td>
<td>30</td>
<td>0</td>
<td>63</td>
<td>Inhaled albuterol</td>
<td>Pulse, heart rhythm, FEV&lt;sub&gt;1&lt;/sub&gt;, walking distance, tremor, oxygen saturation, symptoms</td>
<td></td>
</tr>
<tr>
<td>Wong et al&lt;sup&gt;18&lt;/sup&gt;/1990</td>
<td>Double-blind, crossover/single-dose</td>
<td>Inclusion: other important disorders</td>
<td>10</td>
<td>0</td>
<td>18–40</td>
<td>Inhaled fenoterol, salbutamol, terbutaline</td>
<td>Pulse, potassium, FEV&lt;sub&gt;1&lt;/sub&gt;, bronchial reactivity to histamine</td>
<td></td>
</tr>
<tr>
<td>Yates et al&lt;sup&gt;45&lt;/sup&gt;/1995</td>
<td>Double-blind, crossover/2 wk</td>
<td>Inclusion: mild stable asthma, nonsmoking Exclusion: steroid use within 4 mo</td>
<td>17</td>
<td>0</td>
<td>26</td>
<td>Inhaled formoterol</td>
<td>PC&lt;sub&gt;20&lt;/sub&gt; (methacholine), FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Rescue ipratropium</td>
</tr>
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*<sup>PC<sub>20</sub> = provocative concentration of a substance causing a 20% fall in FEV<sub>1</sub>.</sup>

†Values given as mean or range.
use also has been linked to cardiac arrest (adjusted OR, 1.9; 95% CI, 1.1 to 3.3) and acute cardiac death, with higher risks associated with nebulized and oral treatment (adjusted OR, 2.4; 95% CI, 1.0 to 5.4) compared to metered-dose inhaler treatment (adjusted OR, 1.2; 95% CI, 0.5 to 2.7).\textsuperscript{13,16} These observational studies demonstrate that \beta-agonist use is associated with an increased risk for cardiovascular

### Figure 1
Figure 1. Cardiovascular effects of \beta-agonist use. Heart rate in single-dose trials. \textit{df} = degrees of freedom.

### Figure 2
Figure 2. Cardiovascular effects of \beta-agonist use. Potassium concentrations in single-dose trials. See Figure 1 for abbreviation not used in the text.
events, even when confounding variables are adjusted for. The results of this meta-analysis provide evidence to indicate that the association seen in observational studies may be a causal one.

Over the past 40 years, case reports of adverse cardiovascular events, including ischemia, myocardial depression, atrial fibrillation, ventricular arrhythmia, fatal myocardial contraction band necrosis, and sudden cardiac death, resulting from β2-agonist use have accumulated. β2-Agonists also have been shown to increase ventricular and atrial ectopy, and to prolong the corrected Q-T interval on ECGs. These are all physiologic effects of β2-receptor stimulation in the heart and skeletal muscle.

β-Adrenergic stimulation increases heart rate and myocardial oxygen demand, and causes direct myocardial injury or necrosis that could lead to ischemia, progression of congestive heart failure, or sudden death. Sinus tachycardia is a supraventricular arrhythmia that can signal severe underlying pathology and is associated with a poor prognosis in the

![Figure 3. Cardiovascular effects of β-agonist use. Cardiovascular events in longer duration trials. See Figure 1 for abbreviation not used in the text.](www.chestjournal.org CHEST / 125/6/JUNE, 2004 2317)
presence of underlying ischemia, myocardial infarction, or congestive heart failure. Tachycardia not only is a marker of sympathetic stimulation, which in itself is associated with a poor cardiovascular prognosis, but also directly contributes to cardiac work and strain. Elevated heart rate has been shown to be a strong independent risk factor for the development of cardiomyopathy, coronary artery disease, fatal myocardial infarction, sudden death, cardiovascular mortality, and total mortality.

Hypokalemia occurs with β2-adrenergic stimulation as a result of intracellular shifts of potassium into skeletal muscle. Hypokalemia has been associated with an increased risk for ventricular tachycardia and fibrillation in susceptible patients. In patients with obstructive airway disease, serum potassium levels could be decreased further with the use of corticosteroids and diuretics, and the cardiac effects of hypokalemia could be aggravated by underlying hypoxemia.

The β-adrenergic system has a very tight negative feedback mechanism as an adaptive response to either stimulation or blockade of the receptors. Stimulation results in the uncoupling and internalization of the receptors, which is known as desensitization, and it can occur within a time range of minutes to hours. This is followed by a decrease in receptor density and receptor gene expression, which is known as downregulation, and it develops within hours of stimulation. This tolerance to adrenergic stimulation could explain why the highest risk for adverse cardiovascular events is seen during the initiation of β2-agonist therapy. Conversely, when stimulation is stopped, the receptor begins to recover within a few hours, indicating that the risk for cardiac stimulation is present with continued β2-agonist use, even when used on a relatively regular basis.

This meta-analysis has several limitations that make it difficult to reach definitive conclusions. There was a marked heterogeneity noted in the longer duration trials, despite the fact that no heterogeneity was seen in the results. For example, there was a wide range in study size and duration, the mean age of participants, medications used, and documentation of adverse events. In addition, most of the trials reported a low incidence of adverse events, with large CIs that did not reach statistical significance. Approximately one half of the adverse cardiac events occurred in one trial. However, if this trial were excluded from the analysis, the pooled results would still be significant (RR, 2.15; 95% CI, 1.26 to 3.65).

This analysis provides evidence that β2-agonists, when administered regularly for a few days or for up to 1 year, may increase the risk for adverse cardiovascular events compared to placebo. However, it is not possible to estimate the absolute risk attributed to treatment, as only those trials with at least one event were included in the analysis. Furthermore, almost all of the trials analyzed allowed for as-needed β2-agonist use in the placebo group, which could potentially underestimate the true risk of β2-agonist use compared to no use at all. It is difficult to assess the magnitude of risk for those patients with underlying cardiac conditions or risk factors, as most of the trials in this analysis excluded patients with concomitant cardiovascular disease, abnormal ECG findings, or medical illnesses in general. No information was provided in the trials on concomitant β-blocker use, which could potentially decrease the cardiac risks of β2-agonist therapy.

In this analysis, adverse cardiovascular events were analyzed in two subgroups. Sinus tachycardia was considered to be a minor event, and all other fatal and nonfatal events were combined in the category of major events. The power of the study was not large enough to perform subgroup analyses for each specific cardiac cause. Even when major events were combined, the RR of 1.66 did not reach statistical significance. Despite these limitations, we believe that this analysis should heighten concern over the cardiovascular safety of β2-agonist use in patients with obstructive airway disease.

The competing risks and benefits of β2-agonist use have been a topic of much discussion. β2-agonists have been the mainstay of therapy for obstructive lung diseases since the 1960s, with studies demonstrating sustained improvements in peak flows and respiratory symptoms. Evidence that β2-agonist use is associated with an increase in morbidity and mortality also has been accumulating over the past 50 years. Originally, most of the deaths were thought to be due to cardiac failure with associated underlying ventricular arrhythmias. More recently, evidence has been accumulating indicating that the regular use of β2-agonists also results in tolerance to its bronchodilator and nonbronchodilator effects, and may lead to an increase in asthma exacerbations and deaths.

Once a therapeutic practice is considered to be the standard of care, it often takes numerous studies and many years, if not decades, to transition into a more evidence-based practice. For example, standards of care in the treatment of congestive heart failure have changed drastically since studies showed that β-blockers are beneficial instead of harmful, as originally was thought, and that β1-agonists such as dobutamine can temporarily improve symptoms but at the cost of increased mortality. Many elderly patients with underlying cardiovascular diseases such as congestive heart failure have concomitant obstruc-
tive airway disease. Despite clear evidence that β-blockers reduce mortality in many cardiac conditions, these agents are considered to be contraindicated in patients with obstructive airway disease due to the potential risk for bronchospasm. However, new evidence has shown that cardioselective β-blockers are safe in patients with asthma and COPD, and may actually be beneficial by enhancing sensitivity to endogenous or exogenous β-adrenergic stimulation. 

This analysis reinforces the accumulating evidence that β₂-agonist use leads to an increased risk for adverse cardiovascular events in patients with obstructive airway disease. This is of special concern for those patients with underlying cardiac conditions. In contrast, cardioselective β-blocker therapy is safe in patients with obstructive lung disease and is associated with significant reductions in cardiovascular mortality. To help clarify the issue, long-term trials in patients with obstructive airway disease and concomitant heart disease are needed to evaluate the safety and efficacy of β₂-agonist use compared to therapies using other substances, such as ipratropium, corticosteroids, or β-blockers. Until then, the available evidence needs to be examined closely in an attempt to reassess whether β₂-agonists should be administered to patients with obstructive airway disease, with or without underlying cardiovascular conditions.

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