Heart failure and Chronic Obstructive Pulmonary Disease

The Quandary of Beta-Blockers and Beta-Agonists

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The combination of heart failure and chronic obstructive pulmonary disease presents many therapeutic challenges. The cornerstones of therapy are beta-blockers and beta-agonists, respectively. Their pharmacological effects are diametrically opposed, and each is purported to adversely affect the alternative condition. The tolerability of beta-blockade in patients with mild and fixed airflow obstruction likely extends to those with more severe disease. However, the evidence is rudimentary. The long-term influence of beta-blockade on pulmonary function, symptoms, and quality of life is unclear. Low-dose initiation and gradual up-titration of cardioselective beta-blockers is currently recommended. Robust clinical trials are needed to provide the answers that may finally allay physicians’ mistrust of beta-blockers in patients with chronic obstructive pulmonary disease. Beta-agonists are associated with incident heart failure in patients with pulmonary disease and with increased mortality and hospitalization in those with existing heart failure. These purported adverse effects require further investigation. In the meantime, clinicians should consider carefully the etiology of dyspnea and obtain objective evidence of airflow obstruction before prescribing beta-agonists to patients with heart failure. (J Am Coll Cardiol 2011;57:2127–38) © 2011 by the American College of Cardiology Foundation

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are global epidemics affecting in excess of 10 million patients (1,2). The cornerstones of therapy are beta-blockers and beta-agonists, respectively. The short- and long-term effects of beta-blockade are diametrically opposed: Acute negative inotropy precedes improved left ventricular systolic function. Beta-blockers confer protection from chronically elevated catecholamines and lead to up-regulation of beta-receptors. Reverse remodeling occurs. Beta-agonists exert the reverse pharmacological effects of beta-blockers. Exposure induces down-regulation and desensitization of beta-receptors (3). However, whether acute positive inotropy gives way to longer term left ventricular systolic dysfunction (LVSD) is uncertain.

Although one-third of patients with HF have concurrent COPD (4), few reports have addressed the simple therapeutic questions that interest physicians. Does “severe” or “reversible” airflow obstruction preclude beta1-selective blockade? Is bronchoconstriction lessened by using a beta-blocker with alpha1-antagonist activity? Do beta-blockers improve the prognosis of patients with both conditions? How safe are oral and inhaled beta-agonists in patients with HF? Here, we critically appraise the controversial issues of beta-blockers and beta-agonists in patients with HF and COPD.

Methods

To examine beta-blockers in COPD, the CENTRAL (Cochrane Central Register of Controlled Trials) was searched for randomized, controlled, single- or double-blinded trials. Medical subject heading (MeSH) terms “respiratory tract diseases” and “adrenergic beta-antagonists” yielded 227 studies, 18 of which addressed the review objectives (5–22). Key word searches “chronic obstructive lung disease” and “beta adrenergic receptor blocking agent” or “[beta-blocker name]” identified 2 further studies (23,24). These 20 studies matched the recent Cochrane library systematic review (25). Further information was gathered searching Medline using...
**Guidelines Regarding Beta-Blocker Use in Patients With HF and COPD**

The American College of Cardiology/American Heart Association guidelines for the management of HF advocate “great caution” when using beta-blockers in patients with symptomatic “reactive airways disease” (47,48). No definition of “reactive airways disease” is provided. Concerns stem from reports of acute bronchospasm in asthmatic patients given noncardioselective beta-blockers (49–51). The guidelines also state that “most patients” with COPD “remain reasonable candidates for beta-blockade.” More precise advice is lacking. By contrast, the European Society of Cardiology guidelines clearly state that COPD “is not a contraindication” (1). Low-dose initiation and gradual up-titration is recommended. Furthermore, the guidance indicates, “mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation.”

### Properties of Beta-Blockers Approved for the Treatment of HF

Greater beta<sub>1</sub>-receptor affinity provides a wider division between beta<sub>1</sub> and beta<sub>2</sub>-adrenoceptor blockade, the latter mediating bronchoconstriction. Estimates of beta<sub>1</sub> affinity (so-called cardioselectivity) vary according to methodology. In vitro, beta<sub>1</sub>/beta<sub>2</sub> selectivity ratios have been derived from receptor binding studies in a wide range of tissues using different response measures, agonists, and antagonists. Beta<sub>1</sub> selectivity is demonstrated in vivo through antagonism of biochemical and hemodynamic responses to beta<sub>2</sub> stimuli (52). Table 1 outlines the properties of beta-blockers approved for the treatment of HF (53–56). Cardioselectivity is dose-dependent. Higher plasma concentrations increase competitive antagonism of beta<sub>2</sub>-adrenoceptors with only limited incremental beta<sub>1</sub>-blockade (52,57,58). Beta<sub>2</sub>-blockade may increase airflow obstruction in susceptible patients, possibly through unopposed parasympathetic bronchoconstriction (59,60).

### Randomized Trials of Cardioselective Beta-Blockade in COPD

Only 1 small study has prospectively examined beta-blockade in patients with both HF and COPD (61). The evidence in those with COPD alone informs our daily decisions. Any review of “COPD and HF” must, therefore, objectively appraise beta-blockade in “COPD without HF.” A Cochrane library meta-analysis concluded that long-term cardioselective beta-blockade is safe and well-tolerated in COPD (25,62). This meta-analysis evaluated pulmonary function in 20 randomized, controlled, crossover trials of cardioselective beta<sub>1</sub>-blockers in patients with COPD (Table 2) (5–24). No study included any patients with HF.

The evidence has many limitations. Only 2 studies involved more than 20 patients (15,23), some were only single-blinded (19,20), and others lacked placebo control.

### Table 1: Properties of Beta-Blockers Approved for the Treatment of HF

<table>
<thead>
<tr>
<th>Beta-Blocker</th>
<th>Beta&lt;sub&gt;2&lt;/sub&gt;-Selectivity</th>
<th>Alpha-Antagonism</th>
<th>Intrinsic Sympathomimetic Activity</th>
<th>Lipid Solubility</th>
<th>Route of Elimination</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol (53)</td>
<td>1</td>
<td>+</td>
<td>Moderate</td>
<td>Hepatic</td>
<td>7–10</td>
<td></td>
</tr>
<tr>
<td>Metoprolol tartrate (54)</td>
<td>40</td>
<td>—</td>
<td>Moderate</td>
<td>Hepatic</td>
<td>3–7</td>
<td></td>
</tr>
<tr>
<td>Metoprolol succinate (57)</td>
<td>40</td>
<td>—</td>
<td>Moderate</td>
<td>Hepatic</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Bisoprolol (55)</td>
<td>75</td>
<td>—</td>
<td>Low</td>
<td>Hepatic/Renal</td>
<td>10–12</td>
<td></td>
</tr>
<tr>
<td>Nebivolol (56)</td>
<td>&gt;300</td>
<td>—</td>
<td>High</td>
<td>Hepatic</td>
<td>12–19</td>
<td></td>
</tr>
</tbody>
</table>

Dashes indicate that the property is not present. *The clinical cardioselectivity of metoprolol succinate controlled release/extended release is much higher than that of metoprolol tartrate because of the even beta-blockade achieved with this formulation avoiding peaks and troughs (57). HF = heart failure.
Table 2  Randomized Controlled Trials of Cardioselective Beta-Blockers in Patients With COPD

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>n</th>
<th>Duration</th>
<th>Severe</th>
<th>Reversibility</th>
<th>Placebo Control</th>
<th>Double Blind</th>
<th>Mean FEV₁ (l)</th>
<th>Mean FEV₁ (% Predicted)</th>
<th>Beta-Blocker Route</th>
<th>Route</th>
<th>Dose (mg)</th>
<th>Reduction FEV₁ (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson et al. (5)</td>
<td>9</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Beil and Ulmer (22)</td>
<td>20</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Propranolol</td>
<td>PO</td>
<td>80</td>
<td>—</td>
</tr>
<tr>
<td>Sorbini et al. (24)</td>
<td>8</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>1.9</td>
<td>—</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>50, 100, 150, 200</td>
<td>10%</td>
</tr>
<tr>
<td>Schaanning and Vilsvik (6)</td>
<td>20</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>1.9</td>
<td>—</td>
<td>—</td>
<td>Pracitolol</td>
<td>IV</td>
<td>15</td>
<td>6%</td>
</tr>
<tr>
<td>Perks et al. (12)</td>
<td>10</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.9</td>
<td>—</td>
<td>Atenolol</td>
<td>PO</td>
<td>50, 100</td>
<td>—</td>
</tr>
<tr>
<td>Lammers et al. (7)</td>
<td>8</td>
<td>4 weeks</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>2.4</td>
<td>—</td>
<td>Oxprenolol</td>
<td>PO</td>
<td>100 b.i.d.</td>
<td>0.25</td>
</tr>
<tr>
<td>Tivenius (8)</td>
<td>12</td>
<td>2 days</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.7</td>
<td>50</td>
<td>Metoprolol</td>
<td>PO</td>
<td>50 t.i.d.</td>
<td>0.14</td>
</tr>
<tr>
<td>van der Woude et al. (21)</td>
<td>15</td>
<td>4 days</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>2.4</td>
<td>72</td>
<td>Metoprolol</td>
<td>PO</td>
<td>40 t.i.d.</td>
<td>0.41</td>
</tr>
<tr>
<td>Ranchod et al. (9)</td>
<td>15</td>
<td>3 weeks</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>2.3</td>
<td>—</td>
<td>Atenolol</td>
<td>PO</td>
<td>100 o.d.</td>
<td>0.13</td>
</tr>
<tr>
<td>Adam et al. (10)</td>
<td>10</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.7</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>40 q.i.d.</td>
<td>0.12</td>
</tr>
<tr>
<td>von Wichert (11)</td>
<td>12</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Dorow et al. (13)</td>
<td>12</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.6</td>
<td>—</td>
<td>Bisoprolol</td>
<td>PO</td>
<td>20</td>
<td>NS</td>
</tr>
<tr>
<td>Macquin-Mavier et al. (14)</td>
<td>9</td>
<td>Single</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>80</td>
<td>—</td>
<td>Bisoprolol</td>
<td>PO</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Dorow et al. (15)</td>
<td>34</td>
<td>12 weeks</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.7</td>
<td>—</td>
<td>Acetebutol</td>
<td>PO</td>
<td>400</td>
<td>NS</td>
</tr>
<tr>
<td>McGavin and Williams (16)</td>
<td>9</td>
<td>Single</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.1</td>
<td>40</td>
<td>Metoprolol</td>
<td>PO</td>
<td>100</td>
<td>0.03</td>
</tr>
<tr>
<td>Sinclair (17)</td>
<td>10</td>
<td>Single</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.3</td>
<td>—</td>
<td>Metoprolol</td>
<td>IV</td>
<td>0.12 mg/kg</td>
<td>0.07</td>
</tr>
<tr>
<td>Wunderlich et al. (23)</td>
<td>35</td>
<td>2 days</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>1.3</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>100 b.i.d.</td>
<td>16%</td>
</tr>
<tr>
<td>Butland et al. (18)</td>
<td>12</td>
<td>4 weeks</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>26</td>
<td>Metoprolol</td>
<td>PO</td>
<td>80 b.i.d.</td>
<td>36%</td>
</tr>
<tr>
<td>Fogari et al. (19)</td>
<td>10</td>
<td>1 week</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>1.3</td>
<td>—</td>
<td>Atenolol</td>
<td>PO</td>
<td>100</td>
<td>NS</td>
</tr>
<tr>
<td>Fenster et al. (20)</td>
<td>6</td>
<td>1 week</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>45</td>
<td>—</td>
<td>Metoprolol</td>
<td>PO</td>
<td>50 q.i.d.</td>
<td>6%</td>
</tr>
</tbody>
</table>

b.i.d. = twice a day; COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 s; IV = intravenously; NS = not significant; o.d. = once daily; PO = orally; q.i.d. = 4 times daily; t.i.d. = 3 times daily.
(15,16,19,24). Eleven trials involved a single treatment dose, and only 1 lasted longer than a month (15). The effect of long-term beta-blockade, therefore, is unknown. The 9 “long-term” studies (defined as more than a single treatment dose) involved 147 young, predominantly male patients with moderate airways obstruction (mean forced expiratory volume in 1 s [FEV1]: 1.8 l). Information is particularly limited for beta-blockers conferring benefit in HF. Although many trials used metoprolol, only 2 single-dose studies used bisoprolol (13,14), and none used carvedilol or nebivolol. Most important of all, the evidence lacks the hard clinical endpoints that characterize HF trials.

**Effect of Cardioselective Beta-Blockade in COPD With Reversible Airflow Obstruction**

Of the 20 trials included in the Cochrane meta-analysis, 7 involved patients with reversible airflow obstruction, defined by FEV1 improvement ≥15% following beta2-agonists (10,11,13–15,19,20). Those studies show FEV1 was unaffected by either single dose or longer duration cardioselective beta-blockade (−1.8% and −1.26%, respectively). However, the “long-term” data were derived primarily from a single randomized trial lasting just 12 weeks (15). Celiprolol, a rarely used cardioselective beta-blocker with mild beta2-agonism and alpha2-antagonism, caused no significant change in FEV1 in 34 patients with moderate reversible airflow obstruction.

The longest study to date examining beta-blockade in COPD contradicts these results, but it was not included in the meta-analysis. In a randomized, double-blind, crossover trial (63), 40 patients with mild COPD and significant reversibility received bisoprolol 5 mg or atenolol 50 mg. In that study, FEV1 declined significantly over 6 months by approximately 0.2 l in both treatment arms. Although lacking a concurrent placebo group, lung function parameters normalized during the placebo crossover period, suggesting beta-blockade directly caused bronchoconstriction.

The Cochrane meta-analysis also reported no significant inhibition of beta2-agonist response by cardioselective beta-blockers. However, of the 4 small studies (10,17,19,21), only 2 included patients with significant reversibility (10,19). The minimal influence on bronchodilation is therefore unsurprising. Overall, the long-term effect of cardioselective beta-blockers in patients with COPD and significant reversibility is unknown.

**Effect of Cardioselective Beta-Blockade on Severe Airflow Obstruction**

The same caveats apply to the evidence for beta-blockade in patients with severe COPD. The few existing studies are small, of limited duration, predominantly used metoprolol, had no dose titration, and excluded patients with HF (Table 2). The Cochrane library separately analyzed 6 trials with mean baseline FEV1 <1.4 l or 50% of normal predicted values (16–20,23). No significant change occurred in FEV1 following single-dose or longer-term beta-blocker therapy (−0.71% and −3.11%, respectively) (25). However, the “long-term” results were derived from 2 studies that lasted just 1 week and recruited 16 patients (19,20). Inexplicably, the presented weighted mean difference (−3.11%) failed to incorporate 2 of the 6 referenced studies (18,23). In these, metoprolol reduced FEV1 by 16% in 35 patients, whereas atenolol and metoprolol each significantly reduced FEV1 by approximately 10% in 12 patients.

**Effect of Cardioselective Beta-Blockade on Symptoms**

Only 1 patient in each of the beta-blocker and placebo groups experienced increased respiratory symptoms in the Cochrane meta-analysis (25). The longer duration treatment ranged from just 2 days to 12 weeks. Over short periods, patients may curtail typical daily activities, thus underestimating the effect on symptoms. The perception of respiratory effort and associated distress is subjective and variable with time, reflecting a complex interaction between psychology and physiology (64). Quantification based on physical exertion also fails to reflect mental health and social functioning (65). Only 1 trial formally assessed the effect of beta-blockade on dyspnea and health-related quality of life (61). Over 4 months, bisoprolol titration in 27 patients with HF and concurrent COPD resulted in a nonsignificant improvement in dyspnea and health status assessed using generic and disease-specific questionnaires. These findings require validation in larger cohorts.

Almost all trials evaluating beta-blockade in HF excluded patients with significant pulmonary disease, documented COPD, or bronchodilator therapy (Table 3). The only trial not specifying pulmonary disease or bronchodilators within the exclusion criteria was MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure) (66). Despite this, just 210 (5.3%) of the 3,991 patients enrolled had documented COPD (personal communication, J. Wikstrand, October 2009). Even in beta-blocker trials with less stringent criteria, investigators likely avoid recruiting patients with airflow obstruction. No trial publications report bronchospasm. Whether this reflects genuine tolerability, limited detection strategies, or exclusion of patients with airflow obstruction is unclear. The incidence of respiratory adverse events was similar in the metoprolol and placebo arms of MERIT-HF, including bronchospasm (respectively, 0.3% vs. 0.4%), exacerbation of COPD or bronchitis (0.4% vs. 0.4%), and pneumonia (2.0% vs. 1.9%).

**Effect of Noncardioselective Beta- and Alpha-Blockade on Airflow Obstruction**

Carvedilol is the only noncardioselective beta-blocker approved for treating HF. Many trials in the Cochrane meta-analysis reported adverse side effects with nonselective beta-blockers. Propranolol significantly reduced FEV1 (8–10,16,17,19,21,23), antagonized beta-agonists
increased dyspnea (8,9,16,17,23), and necessitated withdrawal of patients from studies (8,9,16,23). The purported mitigating effect of alpha-blockade is circumstantial at best. Two retrospective Australian analyses assessed carvedilol in patients with HF and airflow obstruction. The first (67) studied 808 consecutive patients commencing open-label treatment, excluding patients with anticipated beta-blocker intolerance. Among 89 patients with coexistent COPD or asthma, 85% tolerated carvedilol. No comments were made regarding the severity and reversibility of airflow obstruction or the reasons for intolerance. The results undoubtedly reflect selection bias rather than true tolerability. The second study (27) examined 31 patients with concomitant moderate COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria (68). FEV\textsubscript{1} was significantly lower with carvedilol (1.85 l/s) than with metoprolol (1.94 l/s) and bisoprolol (2.00 l/s). To conclude, there are no robust data supporting the safety or efficacy of carvedilol, particularly in patients with moderate to severe or reversible airways disease.

### Effect of Beta-Blockade on Mortality in Patients With HF and COPD

In observational studies, use of beta-blockers is consistently associated with better survival in patients with HF and concurrent COPD (46,69,70), a finding corroborated in post–myocardial infarction populations (29,71). In the Val-HeFT (Valsartan Heart Failure Trial) (46), 140 (22%) of 628 participants with physician-recorded COPD received beta-blockers. Mortality over a mean of 23 months was approximately 17%, as opposed to 31% in those with HF and COPD not prescribed beta-blockers (p < 0.001). The VALIANT (Valsartan in Acute Myocardial Infarction Trial) enrolled patients with myocardial infarction complicated by HF, LVSD, or both. A higher proportion of the 1,258 patients with concurrent COPD received beta-blockers (51%), with an associated lower mortality (25% vs. 35%, p < 0.001) (70). Finally, a retrospective Canadian study (69) examined 11,942 elderly patients hospitalized for...
Mortality was lower in those with concurrent COPD who were prescribed beta-blockers, after comprehensive adjustment for age, sex, comorbidity, and propensity scores (hazard ratio: 0.78, 95% confidence interval: 0.63 to 0.95). None of the studies assessed pulmonary function, limiting inference to patients with severe or reversible airflow obstruction. Prescribing bias is inevitable due to perceived or documented intolerance to beta-blockers. This is compounded by recruitment bias in analyses from clinical trials, whose enrolment criteria often excluded patients with significant pulmonary disease. The lower mortality of patients receiving beta-blockers may well reflect less severe lung disease.

### Physiological Rationale for Adverse Beta₂-Agonist Effects

Reduced organ perfusion in HF results in a compensatory increase in adrenergic drive. Epinephrine and norepinephrine stimulate ventricular contraction and increase vascular resistance, maintaining cardiac output and blood pressure. Longer term, increased mechanical stress, myocardial oxygen demand, and ischemia combine with maladaptive adrenergic signaling to depress myocardial function. Beta₁- and beta₂-adrenoceptors mediate norepinephrine toxicity, fibrosis, and necrosis. Down-regulation of beta₁-receptors with relative preservation of the beta₂ subpopulation reduces the beta₁/beta₂ ratio (72). The chronotropic and inotropic responsiveness (and likewise vulnerability) of the failing myocardium to beta₂-agonists thereby assumes greater importance (73,74).

Beta₂-agonists exert numerous unfavorable cardiovascular effects: tachycardia, hypokalemia, QTC prolongation, peripheral vasodilation, disturbed autonomic modulation, and depressed heart rate variability (75–78). In susceptible patients, beta₂-agonists may precipitate ischemic events (79,80). Hypoxia, hypercapnia, acidosis, and excess sympathetic activity in pulmonary disease all potentially amplify these sequelae (75,81,82). When combined with the arrhythmic substrate of left ventricular dysfunction (83), the risk of life-threatening arrhythmias cannot be discounted. However, theoretical concerns may be misplaced. Although beta₂-agonists may exacerbate hypokalemia associated with diuretics (84), hyperkalemia induced by intensive renin angiotensin inhibition may conversely be reduced. Research is needed to define the overall influence of beta-agonists in contemporary populations.

### Cautions Regarding the Adverse Associations Between Beta-Agonists and HF

Beta-agonists are associated with incident HF in patients with pulmonary disease, and with increased mortality and HF hospitalization in those with existing HF or LVSD (Table 4). These reported adverse associations merit careful scrutiny. The evidence was derived from retrospective cohort or case control analyses, all of which equated drug dispensing with drug use. Three fundamental issues under-
minded the conclusions: 1) limited multivariate adjustment; 2) confounding by collinear pulmonary disease; and 3) bias by indication. Multivariable analyses are often restricted in epidemiological studies due to residual confounding by unmeasured covariates. Cardiovascular risk factors and diseases both cluster in patients with COPD, along with underuse of beta-blockers (70,85).

Pulmonary disease may cause cardiac injury through hypoxia, arrhythmias, or even atherosclerotic mechanisms (86). The poor outcomes attributed to beta-agonists may reflect the disease for which they are prescribed. Separating the two is difficult. Dose–response relationships are limited without adjustment for severity of airflow obstruction and cumulative smoking burden (36,80). Patients using more bronchodilators may simply have more severe pulmonary disease. Both physician- and patient-mediated confounding by indication is unavoidable. Physicians may mistakenly prescribe beta-agonists or patients may increase beta-agonist use for symptoms of HF.

Beta-Agonists and Incident HF

Five reports have addressed the association between beta-agonists and incident HF in the general population or those with pulmonary disease (37,38,43,44,87). Prescription event monitoring collates physician reports of adverse events associated with newly launched drugs. Oral bambuterol, but not inhaled salmeterol, was associated with an increased incidence of HF in 8,098 patients when compared with the reference drug nedocromil (risk ratio: 3.41 [95% CI: 1.99 to 5.86], p < 0.001) (43). However, the bambuterol cohort received fewer prescriptions for asthma (57.3% vs. 70.2%) and more “other” indications (12.8% vs. 2.8%). Therefore, bambuterol may have unmasked previously undiagnosed HF, as suggested by the greater risk in the first month of exposure compared with months 2 to 6 (respectively, risk ratio: 4.41 [95% CI: 1.90 to 10.27] vs. 2.67 [95% CI: 1.30 to 5.47]).

Two case-control studies assessed the risk of idiopathic dilated cardiomyopathy defined by echocardiography associated with beta-agonists (38,44). Numbers of events were limited, resulting in wide confidence intervals and statistical uncertainty. Both suffered the inherent failings of case control methodology (88). In Washington, DC, oral beta-agonists were associated with a 3-fold increased risk in 387 patients compared with community-based controls selected using random digit dialing (odds ratio [OR]: 3.4, 95% CI: 1.1 to 11.0) (44). By contrast, a Detroit study (38) of 197 patients observed no significant relationship with inhaled beta-agonists, employing clinic-based controls with ischemic cardiomyopathy. Although differences between oral and inhaled administration are possible, the disparity most likely relates to choice of control groups.

Two nested case-control studies yielded equally conflicting results (37,87). The multicenter ACQUIP (Ambulatory Care Quality Improvement Project) (37) examined health-care records from general medical clinics. Among 782 subjects hospitalized with HF, risk of admission was not related to inhaled beta-agonists after adjusting for age, cardiovascular comorbidity, beta-blocker prescription, and presence of COPD (OR: 1.3, 95% CI: 0.9 to 1.8). By contrast, the adjusted 1-year risk of HF hospitalization was increased among patients with COPD or asthma who were prescribed beta-agonists selected from the Manitoba Health database (OR: 1.74, 95% CI: 1.60 to 1.91) (87). Therefore, whether inhaled beta-agonists are implicated in the development of HF remains uncertain.

Oral Beta-Agonists in HF

Numerous small, short-term controlled studies have examined the oral beta-agonists pirbuterol, prenalterol, salbutamol, and terbutaline in patients with HF (89). The majority demonstrated acute hemodynamic improvements, including ejection fraction, cardiac index, and pulmonary capillary wedge pressure (42). Although uncommon, ventricular arrhythmias were reported (39). Only 2 studies recruited at least 20 patients and lasted longer than a month (35,42). Although symptoms and exercise tolerance improved, no beta-agonist produced a sustained improvement in systolic function. The trials lacked statistical power and were of insufficient duration to identify longer-term impairment of systolic performance.

The risk of arrhythmias is likewise uncertain. Oral sympathomimetic drugs were associated with an increased risk of arrhythmic hospitalization in a case-control study examining 298 patients previously hospitalized with HF (OR: 15.7, 95% CI: 1.1 to 228.0) (45). The confidence intervals were unfortunately wide given the low absolute number of patients receiving systemic sympathomimetics (n = 6). More importantly, the study failed to address the risk of sudden death outside the hospital.

Two large, randomized controlled trials investigated oral xamoterol, a partial beta_1-agonist. The first (33) randomized 433 patients with mild to moderate HF to receive xamoterol, digoxin, or placebo. Xamoterol improved exercise capacity, dyspnea, and fatigue. The Xamoterol in Severe Heart Failure Study aimed to extend these findings in 516 patients with New York Heart Association functional class III and IV symptoms. However, the trial was terminated prematurely due to excess mortality in the xamoterol group within 100 days of randomization (9.1% vs. 3.6%, p = 0.02) (34). Both sudden death and progressive pump failure contributed to the increased mortality.

Respiratory guidelines favor inhaled over oral bronchodilators due to rapid therapeutic action, greater efficacy, and fewer side effects (2). However, neither cardiologic nor pulmonary societies specifically counsel against oral agents in patients with cardiovascular disease (1,2,48,90). This lack of guidance is concerning. In the Val-HeFT, 73% of patients with HF and concurrent COPD were prescribed oral beta_2-agonists (46).
**Nebulized Beta-Agonists in HF**

Nebulized doses are typically 10× greater than standard inhalers. Two facts should be considered. Systemic adverse effects are dose-dependent (91,92), and pulmonary absorption delivers beta-agonists to the heart without first-pass metabolism. Nebulized beta-agonists may precipitate arrhythmias and myocardial ischemia (93,94). Four acute studies recruiting 44 patients in total have administered nebulized beta-agonists to patients with HF (30,32,41,95). No adverse events were reported. In 13 patients, cardiac output and ejection fraction significantly increased within 10 min of inhalation, returning to baseline after 30 min (41). The remaining 3 studies observed a reduction in airflow obstruction following nebulized salbutamol, but no consistent improvement in exercise capacity (30,32,95). Given the limited patient numbers, clinical judgment is paramount. Increasing from 2.5 to 5 mg salbutamol produces only limited incremental bronchodilation (96,97).

**Inhaled Beta-Agonists in HF**

Standard metered-dose beta-agonist inhalers produce only minor systemic and biochemical abnormalities (91,92,98). Whether these contribute to adverse events in patients with HF or LVSD is debatable (36,37). Among 1,529 patients with LVSD identified retrospectively through imaging records (36), all-cause mortality and HF hospitalization within 1 year were associated with beta-agonist use. The risk increased with the average number of canisters dispensed per month. The respective adjusted hazard ratios were: 0.9 and 1.3 (1 canister/month); 1.4 and 1.7 (2 canisters/month); 2.0 and 2.0 (≥3 canisters/month). However, any association is undermined by the indication for beta-agonist use: Increasing dyspnea and resulting beta-agonist prescription may simply reflect worsening HF. Without markers of HF severity, the multivariate model was unable to adjust for such confounding.

In the ACQUIP case-control study (37), beta-agonists were associated with HF hospitalization among those with existing HF (OR: 1.8, 95% CI: 1.1 to 3.0). Adjustment for age, cardiovascular comorbidity, beta-blocker prescription, presence of COPD, and a marker of disease severity (steroid use) reduced the magnitude of association (OR: 1.6, 95% CI: 1.0 to 2.7). Adding smoking status and pack-year history to the multivariate model rendered the relationship nonsignificant (OR: 1.5, 95% CI: 0.8 to 2.8). The findings reinforce concerns that the purported adverse effects of beta-agonists relate to underlying pulmonary disease and clustering of cardiovascular risk factors.

A single study has prospectively investigated inhaled beta-agonists, administering salmeterol 84 μg twice daily to 8 patients with New York Heart Association functional class II or III HF (31). Compared with placebo, salmeterol use improved FEV₁ by 6% (p = 0.01). Concomitant airflow obstruction limits interpretation: mild COPD was not excluded; baseline FEV₁ was reduced in all patients; and smoking history was not documented. The pharmacokinetic data proved more revealing. The steady-state trough and peak concentrations and half-life of salmeterol were at least double those reported in patients with asthma. Physicians must be wary of diminished beta-agonist hepatic metabolism in patients with HF.

**Beta-Agonists in Acute HF**

Inhaled beta-agonists have never been prospectively evaluated in patients with decompensated HF, although the physiological actions are appealing: enhanced cardiac output, reduced peripheral vascular resistance, and bronchodilation (99). However, numerous clinical trials have tested therapies with favorable hemodynamic activity in patients with acute HF, none of which improved mortality (1). Analogies with intravenous inotropic drugs acting through adrenergic pathways are inescapable. Acute improvement may belie myocardial injury leading to increased mortality (1,100). Evidence from 7,299 patients without COPD enrolled in the Acute Decompensated Heart Failure National Registry supports these concerns (101). Bronchodilators were administered to 14.3% of patients and associated with greater requirement for intravenous vasodilators (adjusted OR: 1.40, 95% CI: 1.18 to 1.67) and mechanical ventilation (OR: 1.69, 95% CI: 1.21 to 2.37). Hospital mortality was similar regardless of bronchodilator therapy.

**Interaction Between Beta-Blockers and Beta-Agonists**

The unequivocal pharmacological interaction between beta-blockers and beta-agonists is likely to influence clinical effectiveness. Nevertheless, the evidence supporting an interaction is circumstantial and derives largely from patients experiencing myocardial infarction. The effects of beta-blockers may be attenuated by beta-agonists. Less benefit was apparent in clinical trials using beta-blockers with intrinsic sympathomimetic activity after infarction (102). Beta-blocker use was also not associated with lower mortality among patients receiving concurrent beta-agonists in the Cooperative Cardiovascular Project (29). Conversely, the effects of beta-agonists, both adverse and beneficial, may be attenuated by beta-blockers. The risk of acute coronary syndromes associated with beta-agonists was lessened by concurrent beta-blockade in a case-control study using data from the Veterans Administration’s ACQUIP trial (p for interaction <0.0005) (80). The aforementioned interaction between beta-blockers and beta-agonist bronchodilator response must also be considered. Whereas cardioselective beta-blockers permit bronchodilation, noncardioselective beta-blockers inhibit beta-agonist response.
Clinical Recommendations

Beta-blockers. The uncertainty arising from the paucity of evidence must be balanced against 1 certainty: Beta-blockers markedly improve symptoms and survival in patients with HF. Patients should not be denied therapy that reduces mortality by 35% (66,103,104). COPD (even moderate or severe) is not a contraindication to beta-blockers. Low-dose initiation and gradual up-titration is recommended. Cardioselectivity is paramount; metoprolol, bisoprolol, and nebivolol are candidates.

Beta-agonists. Beta-agonists are associated with increased mortality and hospitalization in patients with HF, and they fail to improve hard clinical endpoints in patients with COPD. Clinicians should only prescribe beta-agonists for clear symptom relief, after carefully considering the etiology of dyspnea and objectively documenting airflow obstruction. Oral beta-agonists should be avoided, and both the dose and frequency of nebulized therapy should be minimized. The possibility of worsening HF must always be considered when beta-agonist use increases in patients with HF and concurrent COPD.

Just as COPD and HF frequently coexist (4), so too do COPD and asthma. Even though randomized controlled trials have established the safety of long-acting beta-agonists in patients with COPD (105), concerns remain regarding safety in patients with asthma that have necessitated label changes under the Food and Drug Administration Amendments Act (106). No prospective study has addressed the safety of long-acting beta-agonists in patients with COPD and concomitant asthma. By contrast, the long-acting anticholinergic bronchodilator tiotropium has proven efficacy in both COPD and more recently asthma (107,108), with reassuring cardiovascular safety data and U.S. Food and Drug Administration approval (109,110). Moreover, another recent large randomized controlled trial has shown tiotropium to be more effective than and equally safe as salmeterol in patients with COPD (111). Patients with HF and concomitant COPD who require regular long-acting inhaled bronchodilators, therefore, should start treatment with a long-acting antimuscarinic rather than long-acting beta-agonists.

Conclusions

The combination of HF and COPD presents complex therapeutic challenges. Many questions remain unanswered. The efficacy of beta-blockade in patients with mild and fixed airflow obstruction likely extends to those with more severe disease, though the evidence is rudimentary. The long-term influence of beta-blockade on pulmonary function, symptoms, and quality of life is unclear. Robust clinical trials are required to provide the answers that may finally allay physicians’ mistrust of beta-blockers in patients with COPD. The potential adverse effects of beta-agonists likewise require further clarification. Studies should be random-ized, placebo-controlled, and of sufficient magnitude to investigate clinical outcomes. The U.S. Food and Drug Administration recently convened to consider the safety of long-acting beta-agonists in asthma (106). The safety of beta-agonists in patients with HF and concurrent pulmonary disease appears equally concerning.

Acknowledgment

The authors would like to thank Dr. Francis Dunn for his valuable contribution and support.

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REFERENCES


Key Words: adrenergic beta-antagonists • chronic obstructive pulmonary disease • heart failure.