Therapeutic Update: Non-Selective Beta- and Alpha-Adrenergic Blockade in Patients With Coexistent Chronic Obstructive Pulmonary Disease and Chronic Heart Failure

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Patients with chronic heart failure (CHF) have a resting restrictive ventilatory defect. Any type of exercise requires patients with CHF to markedly increase their minute ventilation. Patients with chronic obstructive pulmonary disease (COPD) have airflow obstruction that leads to dynamic lung hyperinflation and reduced ventilatory response to exercise. Because exercise is associated with abnormally high minute ventilation in patients with CHF and with a limited minute ventilation increase in patients with COPD, functional capacity is severely impaired in patients with coexistent CHF and COPD. Optimal treatment of both conditions is a prerequisite to maximally improve functional capacity in patients with CHF and COPD. Unfortunately, beta-adrenergic blockade, the current cornerstone of CHF therapy, is frequently omitted in patients with CHF and COPD for fear of inducing bronchoconstriction. Furthermore, when prescribed, beta-adrenergic blockade is often attempted with a moderate dose of metoprolol tartrate, a beta-1-blocker that results in lesser clinical benefits than combined non-selective beta-blockade with carvedilol at the maximally recommended dose. Recent experience indicates that combined non-selective beta- and alpha-blockade with carvedilol is well tolerated in patients with COPD who do not have reversible airway obstruction. Alpha-adrenergic blockade may promote mild bronchodilation that offsets non-selective beta blockade-induced bronchoconstriction in patients with obstructive airway disease. (J Am Coll Cardiol 2004;44:497–502) © 2004 by the American College of Cardiology Foundation

The coexistence of chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) exposes patients to double jeopardy. From a diagnostic standpoint CHF can remain undiagnosed in patients with COPD. The symptoms of CHF and COPD are similar, and the increase in lung volumes associated with COPD hampers palpation of a large heart and/or auscultation of a third heart sound. Furthermore, the acoustic window is frequently poor in patients with COPD, thereby impeding evaluation of cardiac function by two-dimensional Doppler echocardiography. From a therapeutic standpoint, the coexistence of COPD and CHF can be responsible for suboptimal therapy because fear of inducing severe bronchoconstriction leads physicians to withhold beta-adrenergic blockade in these patients. Beta-adrenergic blockade has become the cornerstone of CHF therapy because, aside from cardiac transplantation, it is the only intervention that both reverses cardiac dilation and enhances myocardial contractility (1–4).

Beta-adrenergic blockade-induced bronchoconstriction occurs more often in patients with asthma than in patients with COPD (5–9). Bronchoconstriction also occurs more frequently with non-selective beta-blocking agents than with selective beta-1 agents (10). Selective beta-1–blocking agents do not appear to affect short-term airway function or to increase the incidence of exacerbations in patients with COPD (11), although they significantly reduce mortality after an acute myocardial infarction in these patients (12,13).

The prevalence of COPD in patients with known CHF ranges from 23% to 33% (14,15). The number of patients with COPD and CHF will rise with prolonged life expectancy, as both conditions become increasingly more prevalent with age. As the age-adjusted death rate for COPD continues to rise and the mortality of patients with CHF remains high, the importance of treating both conditions optimally cannot be emphasized enough (16,17).

In this brief review we will first summarize how pulmonary abnormalities in COPD and CHF have a compounding effect on limiting the ventilatory response to exercise. We will then review the experience with beta-1 selective adrenergic blockade in patients with COPD. Last, in view of a recent increased interest in carvedilol, we will review the safety profile of combined non-selective beta- and alpha-adrenergic blockade in patients with COPD and the risk-benefit ratio of this pharmacologic intervention in patients with COPD and CHF (1).
Patients with CHF have a restrictive ventilatory defect and reduced lung diffusing capacity for carbon monoxide (DLCO) (18). Pulmonary congestion, interstitial fibrosis, cardiac enlargement, and respiratory muscle weakness are responsible for the restrictive ventilatory defect (19–22). Of note, the restrictive ventilatory defect regresses after cardiac transplantation, whereas DLCO does not improve (23).

Patients with COPD have progressive airflow obstruction that may be partially reversible (24). Destruction of lung tissue leading to ventilation-perfusion mismatch and increased physiologic dead space results in increased minute ventilation in order to maintain blood gas homeostasis (25). Resting minute ventilation in patients with moderately severe COPD averages 10 l/min, whereas it is 5 l/min in healthy adults.

Restrictive ventilatory defect is the predominant pulmonary abnormality in patients with CHF (26). Their forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) are normal or proportionally reduced. In contrast, the majority of patients with COPD have a greater reduction in FEV1 than in FVC, consistent with an obstructive ventilatory defect (24). However, FVC and FEV1 may be equally reduced in patients with severe COPD due to gas trapping. A near-normal FEV1-to-FVC ratio suggests a restrictive ventilatory defect in these patients. Because a restrictive ventilatory pattern does not exclude the presence of airway obstruction in patients with CHF and COPD, measurement of lung volumes may be required to ascertain the predominant ventilatory defect. Total lung capacity and residual volume are increased with predominant obstruction and are decreased with predominant restriction. Reduced FVC is an independent predictor of cardiovascular morbidity and mortality in healthy subjects (27). It also predicts the heart failure risk in patients with coronary artery disease or left ventricular hypertrophy (28).

The ventilatory response to exercise is abnormal in patients with CHF (29–32). Minute ventilation is 69% greater than normal in patients with CHF whose peak oxygen uptake (V̇O2) is <12 ml/min/kg (26). The mechanisms underlying the abnormally high ventilatory response to exercise in CHF are not well understood. The magnitude of the ventilatory response is inversely related to the partial arterial pressure of carbon dioxide (PacO2) and directly related to peak carbon dioxide production (V̇CO2) and the dead-space-to-tidal-volume ratio (VD/VT) (26). Increased VCO2 and VD/VT and reduced PacO2 without arterial hypoxemia or increased alveolar-arterial oxygen tension gradient are indirect evidences of high but not low ventilation-perfusion ratio mismatch during exercise in CHF (26). Uneven elevation in pulmonary venous pressure is a likely contributor to ventilation-perfusion mismatching. Reduction in perfusion pressure gradient due to elevated pulmonary venous pressure leads to reduced perfusion (26).

During exercise, patients with COPD attempt to further increase minute ventilation. As they cannot increase tidal volume by reducing end-expiratory lung volume due to dynamic hyperinflation, patients with COPD rely on increasing respiratory rate to augment minute ventilation (33,34). Patients with COPD also tend to increase inspiratory flow rate in order to allow more time for exhalation. In order to attain the minute ventilation required to maintain blood gas homeostasis during exercise, patients with CHF need to generate a greater ventilatory response than normal subjects. Airway obstruction prevents patients with coexistent CHF and COPD from increasing ventilatory response during exercise, resulting in severely impaired functional capacity (Fig. 1). The relative contribution of airway obstruction and lung restriction to pulmonary function and gas exchange has not been specifically addressed at rest and during exercise in patients with CHF and COPD. Nevertheless, optimal management of both conditions is essential in order to maximally enhance functional capacity when CHF and COPD coexist.

**EXPERIENCE WITH BETA-ADRENERGIC-BLOCKADE IN COPD**

Most likely for safety considerations, patients with COPD were excluded from most randomized placebo-controlled trials of beta-adrenergic blocking agents in CHF (1–4). Based on case reports of bronchoconstriction induced by non-selective beta-adrenergic blocking agents, CHF guidelines routinely mention COPD as a contraindication to their use in CHF (5–9). Beta-2-receptors predominate on bronchial smooth muscle, whereas beta-1-receptors account for 10% and 30% of adrenoreceptors in submucosal glands and on alveolar walls, respectively (35). Selective beta-1-blocking agents have an affinity for beta-1-receptors that is 20-fold greater than for beta-2-receptors. Selective beta-1-blocking agents are thus less likely to induce bronchoconstriction than are non-selective agents (10). However, selective beta-1-blocking agents appear to lose receptor selectivity at the high end of dose ranging (36,37).

**SELECTIVE BETA-1-ADRENERGIC BLOCKADE**

Unlike non-selective agents such as propranolol and oxprenolol that significantly reduce FEV1 and inhibit the bronchodilator response to the inhaled beta-agonist salbutamol,
selective beta-1–blocking agents such as atenolol and celiprolol do not significantly affect respiratory function or antagonize salbutamol effects in patients with COPD (38). Metoprolol, another selective beta-1–blocking agent, does not significantly affect FEV₁ or FVC at a dose of 200 mg daily when compared with placebo in patients with moderately severe COPD and significant reversible component (39). A single 80-mg dose of propranolol significantly reduces FEV₁ and peak expiratory flow rate in patients with severe COPD, whereas 100 mg of metoprolol does not (40). Whether metoprolol tartrate or metoprolol succinate was used is not specified (39,40). A meta-analysis of 19 randomized placebo-controlled trials of selective beta-1–blocking agents confirms their lack of effects on FEV₁ and bronchodilator response to beta-2-adrenergic stimulation (11). Selective beta-1–blocking agents included in a meta-analysis were atenolol, metoprolol, bisoprolol, practolol, celiprolol, and acebutol. Single doses of selective beta-1–blocking agents were not associated with significant change in FEV₁ compared to placebo, with a weighted mean difference (WMD) of −2.05% (95% confidence interval [CI]: −6.05 to 1.96) in 11 studies involving 141 patients with COPD. Long-term therapy, ranging from 2 days to 12 weeks, with selective beta-1–blocking agents was not associated with significant change in FEV₁ compared to placebo (WMD −2.55% [95% CI: −5.94 to 0.84]) in eight studies involving 126 patients with COPD. Bronchodilator response to beta-2-adrenergic stimulation was not significantly different after single-dose or long-term treatment with selective beta-1–blocking agents (WMD −1.21% [95% CI: −10.97 to 8.56] and WMD −2.0% [95% CI: −13.77 to 9.77], respectively). Selective beta-1–blocking agents do not increase respiratory symptoms in stable patients with severe airflow obstruction, or in those who have a significant reversible obstructive component (11, 38–40). However, the effects of selective beta-1–blocking agents on pulmonary function and symptoms during COPD exacerbation are not available.

**NON-SELECTIVE BETA- AND ALPHA-ADRENERGIC BLOCKADE**

Fewer studies have dealt with agents that exert non-selective beta- and alpha-adrenergic blockade, such as labetalol and carvedilol, in patients with COPD. A maximal dose of labetalol does not affect FEV₁ in these patients (41). Carvedilol has no effect on lung volumes and DLCO in patients with CHF and no obstructive airway disease, whereas it significantly increases left ventricular systolic function at rest (42). Among 89 patients with coexistent COPD or asthma and CHF, 76 tolerated carvedilol well for at least three months (43). Why the remaining 13 patients did not tolerate carvedilol, or how many of them had reversible airway obstruction, was not commented on (43). Thirty-one patients with coexistent CHF and COPD without reversible airflow obstruction receiving a mean dose of 29 ± 19 mg daily of carvedilol were followed for a mean duration of 2.4 years (44). Only one patient did not tolerate carvedilol because of exacerbation of pulmonary disease. Among the 12 patients with coexistent CHF and asthma, 3 did not tolerate carvedilol because of wheezing. At the time of carvedilol withdrawal patients were receiving 6.25, 12.5, and 50 mg of carvedilol, respectively (44). To our knowledge no data are currently available regarding the use of carvedilol in COPD patients with reversible airflow obstruction.

The beneficial effect of beta-adrenergic blockade in patients with coexistent CHF and COPD is difficult to ascertain because such patients have been excluded from all large efficacy trials to date. However, long-term beta-adrenergic blockade after myocardial infarction improves survival to the same extent in patients with and without COPD (12,13). Thus, the American College of Cardiology...
and the American Heart Association updated their guidelines for the treatment of acute myocardial infarction to emphasize that the survival benefit from beta-blockade largely outweighs the risk of adverse events in patients with COPD (45). Cardiac size and function improved similarly in patients with coexistent CHF and COPD and in patients with CHF alone after receiving non-selective beta- and alpha-adrenergic blockade for 24 months (44,46,47).

Selective beta-1-adrenergic blockade enhances maximal exercise capacity in patients with CHF, whereas non-selective adrenergic-blockade does not (48). More complete beta-blockade with non-selective agents may explain the contrasting effect of selective and non-selective beta-blockade on maximal exercise capacity. Quality of life and submaximal response to exercise, which more closely reflect activities of daily living, tend to improve, or at least not worsen, with non-selective agents despite the more complete beta-blockade (49–53).

**MECHANISMS OF BETA-ADRENERGIC BLOCKADE-INDUCED BRONCHOCONSTRICTION**

The mechanisms that mediate beta-adrenergic blockade-induced bronchoconstriction in patients with COPD are not well understood. Beta-adrenergic stimulation inhibits release of acetylcholine, a potent bronchoconstrictor, from cholinergic nerves in human airways (54). In patients with asthma, non-selective beta-adrenergic blockade may cause bronchoconstriction by antagonism of inhibitory presynaptic beta-2-adrenoreceptors on cholinergic nerves (55). Beta-adrenergic blockade-induced bronchoconstriction does not occur in healthy subjects. Their airways are less sensitive to the constrictor effect of acetylcholine than those of asthmatic patients (56). Patients with COPD, unlike those with asthma, experience equal or better bronchodilator responses to anticholinergic agents than to beta-adrenergic agonists (57,58). Beta-2-adrenoreceptors and cholinergic M2 receptors have opposite effects on adenylyl cyclase activity. Thus stimulation of these receptors increases or decreases the cyclic adenosine monophosphate level, respectively. A rise in cyclic adenosine monophosphate level relaxes smooth airway muscle (59). Stimulation of cholinergic M2 receptors reduces adenylyl cyclase activity, thereby counteracting beta-2-agonist–induced smooth airway muscle relaxation (60,61). Accordingly, beta-adrenergic blockade may result in unopposed acetylcholine-mediated bronchoconstriction. Considerable heterogeneity of cholinergic M2 receptors in patients with COPD may explain the variability in the airway response to beta-adrenergic blockade (62).

Alternatively, the bronchoconstrictor effect of beta-blockers may not be directly related to beta-adrenoreceptor blockade (63,64). Alpha-1-adrenergic–blocking agents such as phentolamine and indoramine produce mild bronchodilation in patients with obstructive airway disease and abolish propranolol-induced bronchoconstriction (65–67). Prazosin, an alpha-1–blocking agent, does not affect the respiratory function of healthy subjects and patients with asthma or COPD. To the contrary, prazosin may exert an appreciable bronchodilator effect (68). Thus, partial or complete beta-2-adrenoreceptor blockade with unopposed activation of alpha-receptors may be responsible for bronchoconstriction induced by non-selective beta-blockade. Alpha-1–blocking activity of carvedilol and labetalol may be sufficient to offset beta-adrenergic blockade-induced bronchoconstriction in patients with COPD, but not in patients with asthma (41,69).

**SUMMARY**

Obstructive ventilatory defect in patients with COPD aggravates the impaired ventilatory response to exercise in patients with CHF. Thus, at equal severity of CHF, patients with coexistent COPD and CHF have a lower functional capacity than patients with CHF alone. Accordingly, optimal therapy of CHF is particularly important in patients with coexistent COPD and CHF in order to maximally improve functional capacity. Selective beta-1-adrenergic blockade is routinely preferred to non-selective blockade in patients with coexistent COPD and CHF to minimize the risk of inducing bronchoconstriction. However, recent limited evidence indicates that combined non-selective beta- and alpha-adrenergic blockade is well tolerated by patients with COPD who do not have reversible airway obstruction. Selective beta-1-blockade or non-selective beta- combined with alpha-adrenergic blockade should not be withheld in patients with CHF and COPD without reversible airway obstruction. Past experience with selective beta-1-blockade and recent experience with combined beta- and alpha-adrenergic blockade does not support the fear of inducing bronchoconstriction in these patients. In patients with CHF and COPD with reversible airway obstruction, selective beta-1-blockade remains the preferred approach in the absence of safety data on agents combining non-selective beta- with alpha-adrenergic blockade. Selective beta-1-blockade and non-selective beta- combined with alpha-adrenergic blockade should be avoided during COPD exacerbation until safety data are available.

**REFERENCES**


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