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Challenges in the Management of Patients with Chronic Obstructive Pulmonary Disease and Heart Failure With Reduced Ejection Fraction

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Abstract Chronic obstructive pulmonary disease (COPD) and heart failure with reduced ejection fraction (HFrEF) commonly coexist in clinical practice. The prevalence of COPD among HFrEF patients ranges from 20 to 32 %. On the other hand; HFrEF is prevalent in more than 20 % of COPD patients. With an aging population, the number of patients with coexisting COPD and HFrEF is on rise. Coexisting COPD and HFrEF presents a unique diagnostic and therapeutic clinical conundrum. Common symptoms shared by both conditions mask the early referral and detection of the other. Beta blockers (BB), angiotensin-converting enzyme inhibitors, and aldosterone antagonists have been shown to reduce hospitalizations, morbidity, and mortality in HFrEF while long-acting inhaled bronchodilators (beta-2-agonists and anticholinergics) and corticosteroids have been endorsed for COPD treatment. The opposing pharmacotherapy of BBs and beta-2-agonists highlight the conflict in prescribing BBs in COPD and beta-2-agonists in HFrEF. This has resulted in underutilization of evidence-based therapy for HFrEF in COPD patients owing to fear of adverse effects. This review aims to provide an update and current perspective on diagnostic and therapeutic management of patients with coexisting COPD and HFrEF.

Keywords Heart failure · HFrEF · COPD · Beta blocker therapy · Obstructive lung disease

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Introduction

Heart failure with reduced ejection fraction (HFrEF) and chronic obstructive pulmonary disease (COPD) are commonly encountered chronic conditions. The prevalence of COPD among HFrEF patients ranges from 20 to 32 % [1]. On the other hand, HFrEF is prevalent in more than 20 % of COPD patients [1]. Moreover; the risk of developing HFrEF among COPD patients is 4.5 times higher, after adjusting for age and traditional cardiovascular risk factors [2]. The increased prevalence of COPD and HFrEF in recent years is likely due to improved detection and an increased disease burden with the aging population [3]. The presence of COPD in HFrEF increases burden of co-morbidities, longer hospitalizations, underutilization of evidence-based medicine, and increased mortality [4]. Similarly, the presence of LV dysfunction in COPD patients increases the morbidity and mortality [2].

An analysis from the ARIC (atherosclerosis risk in communities) study underlined a strong inverse association between baseline lung function and incident HFrEF after adjusting for age, gender, race, and smoking status [5], suggesting that low-grade systemic inflammation leads to progression of atherosclerosis and ischemic heart disease as the underlying pathobiology. Moreover, the presence of endothelial dysfunction, elevated inflammatory markers, and accelerated atherosclerosis in untreated patients with combined obstructive sleep apnea and COPD or COPD alone is

associated with higher cardiovascular deaths when compared to well-treated patients [6].

The present review aims to address the diagnostic and therapeutic challenges associated with coexisting COPD and HFrEF. We also discuss a practical diagnostic and therapeutic management based on the current literature.

Diagnostic Considerations

Although COPD and HFrEF commonly coexist, the presence of one condition is often under recognized, and its diagnosis is delayed as COPD and HFrEF share common symptoms like dyspnea, exercise intolerance, skeletal muscle alterations, and overlapping physical signs [7]. Although the presence of jugular venous distension, ankle edema, and hepatomegaly in COPD patients points toward the existence of right ventricular failure, as much as 80 % of concurrent HFrEF may remain unrecognized in elderly patients with COPD, especially in the early phase of disease [8]. This under recognition may be associated with increased morbidity and mortality. Even a mild reduction in FEV1(forced expiratory volume in first second) is associated with increased ischemic heart disease and sudden cardiac death in general population [9]. In general, for every 10 % decrease in FEV1, cardiovascular mortality increases by 28 % after adjustments for relevant confounders [10]. Similarly, among patients with COPD, cardiovascular mortality is quite common [11].

Screening for HFrEF in COPD Patients

Among HFrEF comorbid conditions, COPD is the comorbidity that most delays the diagnosis of HFrEF. When patients with COPD complains of exertional dyspnea or fatigue, these exertional symptoms are often attributed to COPD, and LV dysfunction remains undetected [12]. Electrocardiogram is not specific for diagnosing HFrEF in COPD patients [13]. Chest radiography may not be sensitive for detecting HFrEF coexisting with COPD as the cardiothoracic ratio may remain normal in a hyperinflated chest, and pulmonary edema can be masked by pulmonary vasculature remodeling and radiolucent lung fields [14, 15].

In COPD patients, plasma natriuretic peptides are reliable biomarkers in diagnosing HFrEF. Brain natriuretic peptide (BNP) cut-off point for excluding or detecting HFrEF is 100 pg/ml. BNP levels from 100 to 500 pg/ml may be due to cor pulmonale, moderate LV dysfunction, or both [12]. A BNP level of > 500 pg/ml in a COPD patient with clinical deterioration should raise suspicion of overt HFrEF. However, a BNP level of > 500 pg/ml does not differentiate cardiac from pulmonary deterioration, but indicates that HFrEF therapy should be initiated or upgraded in addition to COPD treatment [12]. An NT-pro-BNP <300 pg/ml excludes HFrEF in COPD patients [16]. For NT-pro-BNP, a value of >450 pg/ml (for patients <50 years) and >900 pg/ml (for patients >50 years) detects HFrEF in COPD patients with acute dyspnea [16]. Although clinical judgment in conjunction with BNP levels leads to a diagnosis of HFrEF in 95 % of patients [16], elevated BNP levels should prompt an echocardiographic assessment for early detection of HFrEF. Radionuclide ventriculography and cardiac MRI are diagnostic modalities of choice when poor acoustic window (due to hyper-inflated lungs) in COPD patients precludes the assessment of LV function by echocardiography.

Screening for COPD in HFrEF Patients

In the absence of overt pulmonary congestion, oxygen desaturation either at rest or during exertion warrants COPD screening with pulmonary function test in patients with HFrEF. Patients with HFrEF have a predominantly restrictive ventilatory defect and reduced lung diffusing capacity for carbon monoxide (DLCO). On the other hand, patients with COPD and an obstructive ventilator defect have a greater reduction in FEV1 than in FVC (forced vital capacity). However, a near normal FEV1/FVC ratio may be seen in severe COPD due to air trapping [17, 18] and should not exclude the presence of COPD. Conversely, transient obstructive ventilatory defect may be seen in acutely decompensated heart failure. The reduction in FEV1 as commonly observed in HFrEF with acute decompensation may lead to overestimation of the severity of airway obstruction in patients with coexisting COPD [19]. Hence, pulmonary function testing is often postponed to 3 months after hospitalization for HFrEF [20].

Measurement of lung volumes may be paramount in ascertaining the predominant ventilatory defect. Total lung capacity (TLC) is increased in COPD patients with predominant airway obstruction whereas HFrEF leads to decreased TLC due to cardiomegaly. As such, TLC may represent the net effect of opposing disorders, and a normal value may not identify mixed ventilator disorder in HFrEF patients with COPD. Residual volume determination provides additional discrimination as residual volume is increased in COPD and unchanged in stable HFrEF [20].

Medical Management

Pharmacological modulation of beta adrenoceptor function is fundamental in the treatment of both COPD and HFrEF. While inhaled beta-2-agonists are the mainstay in the management of COPD, beta-antagonists (BB) have been associated with reduced morbidity and mortality in HFrEF. However, treatment with beta-2-agonists can lead to adverse events in COPD as well as in HFrEF [21]. Few prospective studies and randomized clinical trials have addressed the treatment of patients with COPD and HFrEF. The high prevalence of coincident COPD and HFrEF raises the possibility that COPD may serve as an end point in HFrEF studies and vice-versa. Such approach is in a departure from the conventional

framework that excluded patients with comorbidities from therapeutic clinical trials.

Medical Management of HFrEF in COPD Patients

The coexistence of COPD and HFrEF is often responsible for suboptimal BB use due to perceived fear of inducing bronchospasm. In a study of 799 consecutive hospitalized HFrEF patients, BB use remained unacceptably low with less than 10 % of patients with COPD receiving BB during 5-year follow-up [22]. Only 22 % of patients with both conditions were recently reported to receive BBs [23]. BBs worsen FEV1 and airway hyper-responsiveness in asthma, leading to reluctance in prescribing these agents to COPD patients with HFrEF. Most of BB adverse pulmonary effects are related to withdrawal of beta-2-receptor-mediated bronchodilation. Theoretically, beta-1-blockade should not attenuate beta-2-agonist mediated bronchodilation; however, high-dose beta-1-blockers lose selectivity and can adversely affect airways. Overall, selective beta blockade does not appear to significantly influence respiratory symptoms and functional capacity even in patients with severe COPD and partial reversible airway obstruction; selective adrenergic blockade should not be withheld in HFrEF patients with COPD [24–27]. Furthermore, in the Val-HEFT (valsartan heart failure) study, use of BBs in HFrEF and COPD patients decreased mortality to 17 % over a mean 23 months as compared to 31 % in patients with HFrEF and COPD who were not receiving BBs [28]. On the same note, Van gestel et al. reported the safety and beneficial effect of BB on survival in COPD patients undergoing vascular surgery [29]. Furthermore, selective BB was found to relieve symptoms and reduce exacerbations in patients with COPD [30]. Beta adrenergic blockade-mediated reduction in resting tachycardia might improve exercise tolerance in COPD [31]. BBs may be associated with increased mortality in COPD patients receiving oxygen supplementation [32].

The use of non-selective beta and partial alpha blockade with carvedilol and labetalol appears to be safe in patients with HFrEF and COPD [24, 33]. Substitution of selective with non-selective BB was evaluated in a study of 51 patients with HFrEF and COPD. The substitution was associated with changes in airway function that did not affect functional capacity [34].

Treatment with bisoprolol and carvedilol is equally well tolerated in patients with moderate to severe airflow obstruction and HFrEF [35]. However, bisoprolol had less adverse effect on respiratory parameters than carvedilol. A retrospective analysis of OPTIMIZE-HF (organized program to initiate lifesaving treatment in hospitalized heart failure patients) registry showed that both cardio-selective and non-selective BBs were associated with lower risk-adjusted mortality in HFrEF patients with and without COPD [36]. Moreover, there was no evidence that BB selectivity leads to a difference in outcomes between patients with and without COPD. As nebivolol modulates endogenous nitric oxide production and lowers oxidative stress in addition to selective adrenergic blockade, it may be preferred in COPD patients with HFrEF [37].

The detrimental effects of acute BB use in airway hyperresponsiveness with time may convert into beneficial effects. Long-term use of cardio-selective BBs may reduce mortality and risk of pulmonary exacerbations in COPD patients, even in the subgroups without known cardiovascular diseases [38, 39]. Accordingly, early mild deterioration in pulmonary symptoms or FEV 1 in patients with coexistent HFrEF and COPD should not prompt BB discontinuation. Close observation is recommended, and BB discontinuation is warranted only when pulmonary symptoms persist or worsen [12]. Contrary to conventional belief, selective BBs might be safe even in COPD patients with pulmonary hypertension and right ventricular dysfunction [40–42]. However, the routine use of BB in right ventricular failure patients requires further investigation.

Although long-term beta adrenergic blockade has been reported to be beneficial in single-center studies with limited population of patients with HFrEF and COPD, confirmation awaits a large multicenter randomized placebo-controlled clinical trial. However, the well-known benefits of long-term beta adrenergic blockade in HFrEF raise important ethical issues and question the feasibility of a large placebo-controlled trial. It is noteworthy that long-term treatment with BBs after myocardial infarction improves survival to similar extent in patients with and without COPD [43, 44]. Further studies are needed to systematically understand beneficial effects of long-term beta blockade in COPD patient with HFrEF.

The clinical benefit of beta adrenergic blockade in HFrEF may be in part related to a reduction in heart rate [45]. An analysis of SHIFT (systolic heart failure treatment with I_f inhibitor ivabradine) study population reported the safety of ivabradine use along with BBs in patients with coexisting HF and COPD. Ivabradine similarly decreases heart rate in COPD and non-COPD patients receiving BB [46]. Whether addition of ivabradine to maximally tolerated BB will provide additional clinical benefit remains to be determined in HFrEF patients with COPD.

Treatment with angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers can reduce morbidity and mortality of COPD [47–49] by reducing lung injury and lowering of cardiovascular risk factors [12, 50]. Moreover, ACE inhibition has been shown to prevent smooth muscle atrophy and improve respiratory muscle strength in HFrEF [51]. Hence, ACEI may be particularly beneficial in patients with HFrEF and COPD. Lastly, statins may reduce the decline in pulmonary function [52].

In summary, in COPD patients, HFrEF should be treated according to HF management guidelines, as there is no evidence that HFrEF should be treated differently in the presence of COPD (Table 1).

Table 1 Safety profile and choice of pharmacotherapy for treatment of HFrEF in patient with co-existing COPD

Pharmacological agents used in HFrEF management	Recommendations for patients with coexistent COPD and HFrEF
Cardioselective beta blockers	Safe for use, may help reduce exacerbations, morbidity, and mortality associated with COPD beyond benefits from HFrEF treatment
Non-cardioselective beta blockers	Safe for use, may decrease pulmonary function acutely without any significant clinical deterioration.
Ivabradine	Safe for use
Angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers	Safe for use, may reduce lung injury, and strengthen respiratory muscles
Statins	Safe for use

Medical Management of COPD in HFrEF Patients

The systematic exclusion of COPD patients with co-morbidities from clinical studies hinders the formulation of treatment guideline [53]. The ACQUIP (ambulatory care quality improvement project) study found no association between the use of inhaled beta-2-agonists and the heart failure risk. However, there was a dose-response association (>3 canisters/month; adjusted OR-2.1) between the use of inhaled beat-2-agonists and risk of hospitalization for HF in the COPD cohort with underlying HFrEF [54]. Oral beta-2-agonists should be avoided, and both the dose and frequency of inhaled therapy should be minimized. Decreased hepatic metabolism of beta agonists in HFrEF patients causes accumulation and may partially explain the adverse effects [55]. A patient requiring regular inhaled beta-2-agonists should be switched to an inhaled corticosteroid and/or a long-acting antimuscarinic drug according to cardiovascular safety data [56, 57].

Without history of COPD or asthma, HFrEF patients may develop airway obstruction. Obstruction in airways in HFrEF has been attributed to increased thickness of airway wall due to bronchial mucosal swelling, peribronchial edema and fibrosis, para sympathetic-mediated bronchoconstriction, and alveolar fluid accumulation [58]. Up to 40 % of these patients may have reversible airway obstruction with improvement in pulmonary function after bronchodilator testing [59]. However, whether a bronchodilator response predicts prognosis is not known. Of note, the augmentation of bronchodilator response by BBs via beta-adrenoceptors is due to facilitated stimulation [60]. However, heart rate and myocardial oxygen demand may increase. The efficacy of concomitant BBs to offset the adverse cardiovascular effects of beta-2-agonists in COPD patients with coexistent HFrEF has not yet been assessed in clinical trials.

Systemic inflammation is common to HFrEF and COPD. It is unknown whether reducing systemic inflammation has any effect on cardiovascular risks. A placebo-controlled trial involving 41 COPD patients showed reduction in C-reactive protein and interleukin 6 values by almost 50 % with inhaled steroids [61]. The clinical implications of the reduction in C-reactive protein and interleukin-6 have not been investigated. The use of corticosteroids can increase fluid retention in HFrEF patients. High-dose prednisone (above 20 mg/day) use in COPD patients has a higher risk of decompensated HFrEF [62]. However, inhaled corticosteroids have a lower side effects profile and can be administered according to clinical guidelines. The cardiovascular effects of oral phosphodiestrase-4 inhibitors are largely unexplored. In a pooled analysis, roflumilast was shown to have safe profile [63], but post-marketing data are unavailable.

In summary, modest use of inhaled beta-2-agonists (<3 canisters/month) may be safe in HFrEF patients with COPD.

Table 2 Safety profile and choice of pharmacotherapy for treatment of COPD in patient with co-existing HFrEF

Pharmacological agents used in COPD management	Recommendations for patients with coexistent COPD and HFrEF
Oral beta-2-agonists	Avoid use
Inhaled beta-2-agonists	Limit use, if used frequently consider adding inhaled steroid and/or inhaled anti muscarinic agent
Inhaled anti muscarinic agents	Safe for use
Oral steroids	Avoid long-term use, increased risk of decompensated HFrEF with doses > 20 mg/day
Inhaled steroids	Safe for use
Phosphodiesterase-4 inhibitors	Unknown safety profile in HFrEF
Prophylactic macrolides	Monitor for risk for QT prolongation

Patients with frequent exacerbations or requiring regular inhaled beat-2-agonists should be switched to an inhaled corticosteroid and/or a long-acting antimuscarinic drug (Table 2).

Exacerbation of Respiratory Symptoms in Patients with Coexisting COPD and HFrEF

Up to a third of hospitalized HFrEF patients suffer from COPD and one in every five decompensated COPD patients has HFrEF [1, 64, 65]. In patients with coexisting COPD and HFrEF, the exacerbation of respiratory symptoms may be difficult to investigate. In addition, acute worsening of one condition may lead to decompensation of the other due to shared pathophysiological mechanisms. COPD exacerbation is defined as an acute worsening of the patient's respiratory symptoms leading to a medication change and/or hospitalization [66]. The biomarkers of myocardial damage may be found without overt clinical manifestations of LV dysfunction and are associated with increased mortality in COPD patients with acute exacerbation [67]. MicroRNAs have recently received interest as candidate biomarkers of heart failure in patients presenting with dyspnea. Further work is required to fully understand the diagnostic utility and function of these circulating microRNAs, both independently and in combination with other biomarkers [68]. Novel and reliable biomarkers of the mechanisms that underlie exacerbation of respiratory symptoms are clearly needed.

Continuing selective BBs is apparently safe during a hospitalization for COPD exacerbations [69]. Drunsfield noted reduction in-hospital mortality with BB use in 825 patients hospitalized for COPD exacerbation. The treatment group was older, had longer length of stay, and greater prevalence of heart failure [70]. However, the long-term safety of BBs has not been investigated in COPD patients with recent exacerbations. Acute COPD exacerbations are associated with fluid and salt retention that may be exacerbated by the use of BB [71].

The safety of inhaled beta-2-agonists in symptomatic patients with HFrEF and COPD has not been explored in prospective studies. Data from ADHERE-EM (acute decompensated heart failure national registry emergency module) suggested that inhaled beta-2-agonist use in decompensated HFrEF without COPD may be associated with unfavorable outcome [72]. A retrospective review of discharged patients with decompensated HFrEF showed a high rate of adverse outcomes in patients who received inhaled beta-2-agonists during the first two hospital days [73].

The worsening of respiratory symptoms when COPD and HFrEF coexist should be called "exacerbation of respiratory symptoms" rather than COPD or HFrEF exacerbation. Such approach is not only semantic but also it may stimulate investigation of the complex mechanisms that underlie deterioration in patients with coexisting HFrEF and COPD [74].

Conclusion

The coexistence of COPD and HFrEF is commonly encountered in clinical practice. The prevalence is expected to rise further with the aging population. Shared symptoms and opposite modulation of the beta adrenergic pathway pharmcotherapeutics cause delayed recognition and under treatment the inciting entity. Natriuretic peptide levels should be obtained in COPD patients who remain symptomatic despite optimal management. An elevated level (>100 pg/ml) should prompt confirmation with optimal cardiovascular imaging including echocardiogram or cardiac MRI. Similarly, presence of hypoxia at rest or during exertion should prompt pulmonary function testing and/or thoracic imaging to evaluate for the presence of COPD in HFrEF. Beta blockade is safe in patients with COPD and HFrEF. However, it should be avoided in patients receiving home oxygen therapy. Oral beta-2-agonists and regular use of inhaled beta-2-agonists should also be avoided in these patients.

Compliance with Ethical Standards

Conflict of Interest Abhishek Jaiswal; Astha Chichra; Vinh Q. Nguyen; Taraka V. Gadiraju; and Thierry H. Le Jemtel declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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