

## Update in diagnosis and therapy of coexistent chronic obstructive pulmonary disease and chronic heart failure

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### ABSTRACT

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) frequently coexist in clinical practice as they share the same risk factors. The manifestations of COPD and CHF are similar. Exertional dyspnoea, easy fatigability and reduced exercise tolerance are common to COPD and CHF and required careful interpretation. Pulmonary function tests, plasma natriuretic peptides, echocardiography and cardiovascular magnetic resonance imaging should be carried out to acquire the objective evidence of pulmonary and cardiac function when necessary. Robust studies indicate that patients with COPD tolerate the cardioselective  $\beta$ -blockers well, so it should not be denied to CHF patients with concomitant COPD. Low-dose initiation and gradual uptitration of cardioselective  $\beta$ -blockers is currently recommended. However,  $\beta_2$ -agonists should be used with cautions in COPD patients with CHF, especially in acute exacerbations. Statins, angiotensin-converting enzyme inhibitors, and angiotensin-receptor blockers may reduce the morbidity and mortality of the patients with COPD.

### KEY WORDS

Chronic obstructive pulmonary disease; chronic heart failure; beta blockers

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### Introduction

Chronic obstructive pulmonary disease (COPD) and chronic heart failure (CHF) are global epidemics, each affecting in excess of 10 million patients. Both conditions incur significant morbidity and mortality, and present significant challenges to healthcare providers (1). Moreover, COPD and CHF also frequently coexist in clinical practice as they share the same risk factors, including cigarette smoking, advanced age and systemic inflammation (2,3).

#### *Prevalence of CHF in patients with COPD*

COPD is a frequently concomitant comorbidity in patients with CHF. And it is also an important and independent risk

factor for atherosclerosis (4,5). In COPD, CHF is prevalent in more than 20% of patients (6,7). The risk ratio of developing CHF is 4.5 (95% confidence interval 4.25 to 4.95) in COPD patients compared to age-matched controls without COPD after adjustments for cardiovascular risk factors (7,8). The rate adjusted hospital prevalence of CHF is 3 times greater among patients discharged with a diagnosis of COPD compared with patients discharged without mention of COPD (8).

#### *Prevalence of COPD in patients with CHF*

In return, in patients with CHF the prevalence of COPD ranges from 20% to 32% (7,9). The reported prevalence of COPD in patients with HF ranges widely from 11% to 52% in North America and from 9% to 41% in European cohorts (1,10). In addition, COPD is more common in male compared with female HF patients and in urban compared with rural areas (1). Moreover, there is a non-linear relationship between age and frequency of concurrent COPD in patients with HF. It is lowest in the young and very elderly, under 55 and over 85 years of age, respectively (10).

### Diagnosis

The prevalence of CHF in patients with COPD and *vice versa* is well documented. Patients concurrent with COPD and CHF have much worse prognosis in comparison with patients

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with individual disease (2). COPD patients with concurrent CHF have twice the risk of dying from a cardiovascular cause than those without CHF (11). Hence, it is very important to recognize the concurrent of COPD and CHF.

### **Symptoms**

The clinical manifestations of COPD and CHF are similar (1-3,8,10). Exertional dyspnoea is the frequent symptom common to COPD and CHF. Fatigue is also a common, if nonspecific, complaint of patients with COPD and CHF, which together with exertional dyspnoea result in marked activity intolerance. Apart from dyspnoea and fatigue, depression and anxiety are also common in both COPD and CHF.

However, new onset orthopnoea, nocturnal cough, paroxysmal nocturnal dyspnoea or acute pulmonary edema, easy fatigability and reduced exercise tolerance in the absence of evidence of chest infection in COPD patients should arouse a suspicion of HF (3). Symptoms of angina tilt the diagnosis in favor of coronary artery disease with HF. In acute onset dyspnoea, absence of cough or change in character of sputum should lead to a search for causes other than acute exacerbations of COPD, including acute left ventricle failure (3).

### **Signs**

The pulmonary examination and cardiac examination in patients coexistence of COPD and CHF are usually unremarkable because of the lung hyperinflation.

Crackles may be heard in COPD due to opening of small airways. Wheeze is audible in CHF due to airflow limitation in the smaller airways, while crackles of pulmonary edema may be inaudible in a hyperinflated chest (3). Presence of jugular venous distention, ankle edema, and hepatomegaly in COPD should arouse the suspicion of right ventricular failure (1,3). Presence of a loud P2 and left parasternal heave point towards cor-pulmonale while a pansystolic murmur over the mitral area may be due to a papillary muscle dysfunction in coronary artery disease (3).

In a word, the signs and symptoms of coexistence COPD and CHF are neither specific nor sensitive. Additional laboratory testing should be performed in a patient with COPD or CHF.

### **Chest radiography**

Chest radiography is insensitive for detecting the coexistence. On one hand, the cardiothoracic ratio may remain in the normal range as the heart tends to become long and narrow in a hyperinflated chest (3). On the other hand, pulmonary vascular remodelling and radiolucent lung fields mask the typical alveolar shadowing of pulmonary oedema (1). But chest radiography may be useful for detecting additional disease.

### **Pulmonary function tests (PFTs)**

Objective evidence of airflow obstruction is mandatory for diagnosing COPD. According to the GOLD criteria : a post-dilatory ratio of forced expiratory volume in 1s and forced vital capacity of less than 0.7 ( $FEV_1/FVC < 0.7$ ) measured with spirometry confirmed the diagnosis of COPD (12). Recently, ACP, ACCP, ATS and ERS recommend that spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms, and spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms (13).

CHF has a mixed effect on pulmonary function. Patients coexistence with COPD and CHF have combined obstruction and restriction in PFTs (14,15). However, Lung function can improve after treatment of CHF. With diuresis, mean  $FEV_1$  improves by up to 35% and returns to normal. So in patients with CHF, it is advisable to repeat spirometry after patients have been titrated to recommended doses of CHF medication to make a final diagnosis of COPD (15).

### **Plasma B-type natriuretic peptides (BNP)**

Plasma B-type Natriuretic Peptides is a rapid and sensitive biomarker for diagnosing CHF from patients with COPD (16). A single cut point for BNP to exclude/detect CHF is  $</\geq 100$  pg/mL. CHF is unlikely when BNP levels are  $< 100$  pg/mL. In COPD patients, BNP levels ranging from 100 to 500 pg/mL indicate right-sided (R) heart failure, moderate left-sided heart failure, or both and the need to initiate therapy with angiotensin-converting enzyme (ACE) inhibitors and possibly loop diuretics. Although not specifically tested in patients with a history of COPD, BNP  $> 500$  pg/mL is suggested by others to indicate acute HF in COPD and CHF therapy should be initiated (3,5,8,17). When BNP added to clinical judgment, 95-100% of the patients are correctly diagnosed (3,17). For NT-proBNP, a value of  $< 300$  pg/mL to exclude HF, and of  $> 450$  pg/mL for patients  $< 50$  years and of  $> 900$  pg/mL for those  $\geq 50$  years to detect HF is tested in patients with previous COPD presenting with acute dyspnoea (17). However, the recent NICE guidelines recommend that a BNP level  $> 400$  pg/mL or an NT-proBNP level  $> 2,000$  pg/mL should arouse the suspicion of HF (18).

### **Echocardiography**

Echocardiography is a valuable tool to study the structure and the function of the heart noninvasively and safely. The NICE guidelines recently recommend that the echocardiogram and the specialist clinical opinion should be referred within 2 weeks if BNP  $> 400$  pg/mL or NT-proBNP  $> 2,000$  pg/mL or within 6 weeks if BNP 100-400 pg/mL or NT-proBNP 400-

2,000 pg/mL (18). A normal echocardiogram excludes CHF. No CHF therapy is needed. The diagnosis of diastolic heart failure needs to be considered in COPD patients with LV ejection fraction >40% and abnormal LV mass or enlarged left atrium by echocardiography or impaired LV filling by radionuclide ventriculography (RNV), and the response to ACE inhibitors and loop diuretics needs to be closely monitored. When patients with COPD have an LV ejection fraction  $\leq$ 40%, full CHF therapy including beta-adrenergic blockade is recommended (8).

### Cardiovascular magnetic resonance imaging (CMR)

Cardiovascular magnetic resonance imaging (CMR) is the accepted reference standard for measuring LV volumes and ejection fraction (1). It offers a powerful tool to detect or exclude CHF in stable patients with mild to moderate COPD. Combination of CMR measurements of left ventricular ejection fraction, indexed left and right atrial volume, and left ventricular end-systolic dimensions provide high added diagnostic value beyond clinical items (ROC-area 0.91) for identifying CHF. Right ventricular mass divided by right ventricular end-diastolic is higher in COPD patients with CHF than in those without concomitant CHF. Disadvantages of CMR include the acquisition time, limited availability, and a higher price than echocardiography (19). Professional imaging societies recommend CMR to evaluate LV function in HF patients with technically limited echocardiogram images (1).

## Therapy

### Oxygen therapy

Oxygen therapy is one of the principal nonpharmacologic treatments that improve survival in COPD. Recently, Global initiative for chronic obstructive lung disease (GOLD) recommends to introduce long-term oxygen therapy (LTOT) in patients with Stage IV: Very Severe COPD who have: PaO<sub>2</sub> is at or below 7.3 kPa (55 mm Hg) or SaO<sub>2</sub> is at or below 88%, with or without hypercapnia; or PaO<sub>2</sub> between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg), or SaO<sub>2</sub> of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%) (20). Currently, no evidence exists that long-term oxygen therapy reduces breathlessness or the frequency of clinical events (such as admission to hospital or mortality) in patients with CHF (21). But we still should prescribe oxygen therapy in patients hospitalized with severe CHF and COPD exacerbation as it may improve oxygenation. Patients with COPD and CHF may often experience isolated nocturnal hypoxaemia, more studies are needed to evaluate whether nocturnal oxygen therapy may be of benefit to these patients.

### Antibiotics

Infection is the most common causes of an exacerbation of COPD and CHF. In COPD patients with or without CHF, the presence of fever, purulent sputum, leukocytosis and a new or changing radiographic infiltrate is sufficient indication for starting empirical antibiotic treatment. If an infectious exacerbation does not respond to the initial antibiotic treatment, a sputum culture and a drug susceptibility test should be performed. Once the etiologic agent is known, treatment should be altered to target the specific pathogen. A diagnosis of pulmonary embolism should be considered in patients who do not respond to appropriate antimicrobial treatment.

### $\beta$ -blockers

Despite clear evidence of the effectiveness of  $\beta$ -blockers in the management of patients with CHF, the use of these agents has traditionally been contraindicated in COPD, mainly because they might cause acute bronchospasm, increase airway hyperresponsiveness and worsen respiratory symptoms. Recently, the NICE and European Society of Cardiology (ESC) guidelines clearly state that COPD is not a contraindication to the use of  $\beta$ -blockers, and mild deterioration in pulmonary function and symptoms should not lead to prompt discontinuation. Low-dose initiation and gradual uptitration is recommended (18,22).

$\beta$ -blockers can be divided into two kinds, cardioselective  $\beta$ -blockers and noncardioselective  $\beta$ -blockers. The cardioselective  $\beta$ -blockers have greater selective affinity for  $\beta_1$ - than  $\beta_2$ -receptors, whereas the noncardioselective  $\beta$ -blockers have similar affinity for both  $\beta_1$ - and  $\beta_2$ -receptors as well as  $\alpha$ -blocking capacity. However, cardioselectivity is dose-dependent. Higher plasma concentrations increase competitive antagonism of  $\beta_2$ -receptors with only limited incremental  $\beta_1$ -blockade (23).

### Effect of $\beta$ -blockers on lung function

There is increasing evidence suggesting that respiratory symptoms and FEV<sub>1</sub> are not significantly worsened by cardioselective  $\beta$ -blockers in COPD. In a recent meta-analysis of the relation between cardioselective  $\beta$ -blockers and COPD, no significant differences were noted in FEV<sub>1</sub> or respiratory symptoms between patients treated with a cardioselective  $\beta$ -blocker and those treated with a placebo, even in patients with severe COPD (24).

Carvedilol is the only noncardioselective  $\beta$ -blocker approved for treating CHF, and tolerated by the patients coexistent with CHF and COPD. In a randomized, open label, triple-crossover trial examined 35 patients with coexistent COPD according to GOLD criteria, FEV<sub>1</sub> was significantly lower with carvedilol

(1.85 L/s) than with metoprolol (1.94 L/s) and bisoprolol (2.00 L/s). But it suggested that switching from  $\beta_1$ -blockers to carvedilol was safe (9). Hence, more studies are needed to ascertain the effect of noncardioselective  $\beta$ -blocker on COPD.

### **Effect of $\beta$ -blockers on mortality and risk of exacerbation in COPD**

Use of cardioselective  $\beta$ -blockers is consistently associated with better survival in patients with CHF and concurrent COPD in observational studies (25,26). In the Val HeFT (Valsartan Heart Failure Trial), 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 ( $P < 0.001$ ) (25). Dransfield and co-workers assessed 825 inpatients admitted for acute exacerbations of COPD, and noted that the use of  $\beta$ -blockers was associated with a reduced rate of mortality in hospital (OR=0.39; 95% CI, 0.14 to 0.99). The benefit of  $\beta$ -blockers was observed despite patients who were treated being older, having longer hospital stays, and having a greater prevalence of congestive heart failure and cerebrovascular disease, all factors that were independent predictors of in-hospital mortality (26).

Moreover, a recent observational cohort study showed that long-term treatment with  $\beta$ -blockers might improve survival and reduce the risk of an exacerbation of COPD in the broad spectrum of patients with a diagnosis of COPD, including those who have COPD with but, importantly, also without overt cardiovascular comorbidities (27). Short and colleagues investigated the effect of  $\beta$ -blockers added to specific treatment regimens for COPD across the spectrum of disease severity. They assessed 5977 patients aged  $>50$  years with a diagnosis of COPD and noted that  $\beta$  blockers may reduce mortality and COPD exacerbations when added to established inhaled stepwise therapy for COPD, independently of overt cardiovascular disease and cardiac drugs, and without adverse effects on pulmonary function (28). However, we need prospective studies to ascertain any beneficial effect of  $\beta$ -blockers on COPD related outcomes.

In summary, COPD (even moderate or severe) is not a contraindication to  $\beta$ -blockers (23,29). It is recommended to only use those  $\beta$ -blockers that are more selective for the  $\beta_1$ -AR at the lowest dose and to titrate them slowly with attention to lung function and symptoms, adding an inhaled antimuscarinic agent when bronchodilation is needed (29).

### **Bronchodilators in patients with CHF**

Inhaled  $\beta_2$ -agonists induce adverse cardiac effects in COPD patients with pre-existing cardiovascular disease. In particular,

the adverse effects of  $\beta_2$ -agonists are likely to be exacerbated in COPD patients with coexistent CHF (29). Hawkins *et al.* assessed 7,599 patients with symptomatic HF to receive candesartan or placebo. Bronchodilator use was associated with increased all-cause mortality, cardiovascular death, HF hospitalization, and major adverse cardiovascular events. The adverse outcomes were consistent in patients with reduced and preserved systolic function. But no significant interaction was observed between bronchodilators and beta-blockade with respect to outcomes (30). However, a recent rat model of dilated cardiomyopathy indicated that a combination of  $\beta_2$ -AR agonists and a  $\beta_1$ -AR blocker is more effective than  $\beta_1$ -AR blocker alone and as effective as  $\beta_1$ -AR blocker with ACE inhibitor with respect to treatment of dilated cardiomyopathy. This combined regimen of  $\beta_2$ -AR agonists and a  $\beta_1$ -AR blocker might be considered for clinical testing as alternative or adjunct therapy to currently acceptable CHF arsenal (31).

Currently, clinicians should only prescribe  $\beta_2$ -agonists for clear symptom relief, after carefully considering the etiology of dyspnoea and objectively documenting airflow obstruction. Oral  $\beta_2$ -agonists should be avoided, and both the dose and frequency of nebulized therapy should be minimized (23).

### **Statins and ACE inhibitors**

Observational studies suggest that statins, angiotensin-converting-enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs) can reduce the morbidity and mortality of the patients with COPD (32,33). A time-matched nested case-control study showed that statins, ACE inhibitors, and ARBs may have dual cardiopulmonary protective properties, thereby substantially altering prognosis of patients with COPD. The combination of statins and ACE inhibitors or ARBs was associated with a reduction in COPD hospitalization and total mortality rates in cohorts with high and low cardiovascular risks. Furthermore, this drug combination reduced myocardial infarction rate in the COPD cohort with high cardiovascular risk, independently of the concomitant use of steroids (32). Mortensen *et al.* reported that the use of statins and ACE inhibitors prior to admission was associated with decreased mortality in subjects hospitalized with a COPD exacerbation (33).

Moreover, a recent prospective study followed up 245 patients admitted to hospital for exacerbations of COPD (ECOPD) for one year. It showed that there was no effect of statins on either 30-days or 1-year mortality. Patients receiving statins presented a lower total number of ECOPD during the 1-year follow up. After proper adjustments, the use of statins was associated with a lower risk for ECOPD and severe COPD. The group of statins presented better improvement in health-related quality of life at 2, 6 and 12 months (34).



## Conclusions

COPD and CHF frequently coexist in clinical practice, and importantly influence each other in both management and prognosis. Clinical symptoms and signs require careful interpretation. Objective evidence of each condition should be obtained. The cardioselective  $\beta$ -blockers should not be denied to the patients who have coexistent COPD and CHF. Low-dose initiation and gradual uptitration of cardioselective  $\beta$ -blockers is currently recommended. However,  $\beta_2$ -agonists should be used with cautions, especially in acute exacerbations. Statins, ACE inhibitors, and ARBs may reduce the morbidity and mortality of the patients with COPD.

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