Chronic obstructive pulmonary disease and heart failure: common diseases of the elderly, frequent non-recognition and the value of specialist referral

C. Vitale¹, V. Conti¹, A. Maglio¹, G. Pelaia², A. Molino³, A. Vatrella¹

¹ Department of Medicine, Surgery and Dentistry “Scuola Medica Salernitana”, University of Salerno, Italy; ² First Division of Respiratory Disease, University “Federico II” of Naples, Italy; ³ Department of Medical and Surgical Sciences, Section of Respiratory Diseases, University “Magna Græcia” of Catanzaro, Catanzaro, Italy

Chronic Obstructive Pulmonary Disease (COPD) and Heart Failure (HF) are major and increasing public health problems worldwide. Both conditions are common diseases of the elderly and often coexist. Unfortunately their coexistence frequently remains unrecognized mainly due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD. The coexistence of HF and COPD presents many diagnostic challenges. Several tests can be performed to assist in the diagnosis of each disease. Assessment of left ventricular function by transthoracic echocardiography is mandatory for diagnosing HF, while magnetic resonance imaging is the modality of choice in those with limited acoustic windows. On the other hand, objective evidence of airflow obstruction, demonstrated when clinically euvoletic is mandatory for diagnosing COPD. Greater collaboration is required between cardiology, pulmonology, and general practitioners. Both are chronic progressive diseases and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early.

Key words: Chronic obstructive pulmonary disease, Heart failure, Elderly

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and heart failure (HF) are major and increasing public health problems worldwide. Both conditions are common diseases of the elderly and show high morbidity and mortality rates, contributing enormously to the global burden of disease and result in an economic and social burden ¹³. Although both diseases have been extensively studied separately, clinicians often fail to recognize one syndrome in the presence of the other, mainly due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD ⁴.

According to the available evidences, COPD and HF often coexist and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early. The present review focuses mainly on the diagnostic challenges presented by the combination of COPD and HF.

EPIDEMIOLOGY OF COEXISTING COPD AND HEART FAILURE

The prevalence of the COPD and HF combination is variable, depending on the population studied (community,
outpatient or hospitalized and on the diagnostic criteria applied. The coexistence of the two conditions is further supported by shared risk factors, notably age and smoking.

Epidemiological studies reveal that the incidences of both COPD and HF increase with age. Although both can be considered diseases of the elderly, COPD develops on average 10 years earlier than HF (>55 vs >65). The incidence of HF doubles with each decade of life. About 50% of HF cases are observed in patients older than 70 years, with a prevalence reaching nearly 10% in patients older than 80 years. Regarding COPD, existing prevalence data ranges from 7.8% to 26.1% and become higher in the elderly population. It was reported that the prevalence of concurrent COPD in patients with HF increases until around 75 years of age, and declines thereafter. This non-linear relationship is probably due to the presence of COPD that may reduce survival beyond this age.

The prevalence of HF in elderly COPD patients is reported to be 21-31%, while the reported prevalence of COPD in HF varies considerably depending on the population studied, ranging from 7% to 13% in HF outpatients and from 9% to 51% in hospitalized HF patients. However, most studies of the prevalence of coexistent COPD and HF have established diagnosis criteria in a retrospective way and, in most cases, have used a no appropriate definition of both COPD and HF, as they had not been based on GOLD criteria and reproducible echocardiographic parameters. Macchia et al., in a prospective cohort study, found a prevalence of 17% of left ventricular dysfunction in patients with clinical and spirometrically confirmed COPD diagnosis and a prevalence of 37.3% of airway obstruction in patients with echocardiographically confirmed HF.

Recently two larger studies have shown that the airflow obstruction observed in patients with HF is dynamic; thus spirometry might overestimate the presence of COPD in patients with HF and serial measurements are mandatory in order to minimize the risk of false positive COPD. In this regard, Dalsgaard et al. examined 593 HF patients with spirometry at their first visit and after optimal medical treatment for HF was achieved. The prevalence of airway obstruction was 39%, although at the baseline spirometry only 12% of patients had a clinical diagnosis of COPD.

**PATHOPHYSIOLOGICAL MECHANISMS**

Several studies have shown that patients with COPD are at increased risk of cardiovascular disease. The underlying pathophysiological mechanisms that are responsible for the increased cardiovascular risk in COPD remain unclear but might involve several factors such as: biological (hypoxemia, endothelial dysfunction, arterial stiffness) and/or functional (emphysema, hyperinflation), neurohumoral and genetic (metalloproteinases, telomere shortening).

The cardiac abnormality related with COPD has traditionally been right ventricular dysfunction. In the past, heart failure was considered as rather uncommon in COPD, and whenever present was thought to occur as right-sided heart failure. However, the prevalence of true “cor pulmonale” or right-sided heart failure in COPD has been shown to be rather low but might be higher in more severe cases with COPD.

More recent studies have reported that the left ventricle may also be affected in COPD and have addressed the coincidence of both COPD and HF and their potential clinical interrelations thereafter. The relationship between COPD and HF is not completely clear; nevertheless, the high rate of coexistence of COPD and HF suggests that these two conditions, although aetiologically distinct, share common pathophysiological mechanisms.

These chronic diseases share smoking and age as risk factors, and the association of low-grade systemic inflammation. A growing body of evidence indicates that systemic inflammation could be the common pathway leading to the high prevalence of multiple chronic diseases in the same patient. Therefore chronic systemic inflammation seems to be a critical link between COPD and HF. High circulatory values of proinflammatory cytokines have been found in patients with COPD and HF, such as tumour-necrosis factor (TNF)–α, interleukin-1 (IL-1), and IL-6; these cytokines might accelerate and perpetuate disease progression and exacerbation of both diseases.

Mechanisms by which systemic inflammation may lead to heart failure in COPD patients include accelerated atherosclerosis (plaque genesis, progression and rupture) leading to the development of ischemic heart disease.
In epidemiologic studies and clinical cohorts, OSA has also been associated with an increased risk of death, mainly because of cardiovascular causes. Indeed, it has been suggested that the number of cardiovascular deaths in patients with untreated overlap syndrome is higher when compared with overlap treated patients, and also higher than those with COPD only. It is now recognized that COPD and HF are systemic diseases with profound effects on multiple peripheral tissues including skeletal muscle. Skeletal muscle alterations in patients with COPD and HF include a decrease in muscle mass, size, and diameter. The mechanisms involved in muscular atrophy in both diseases are unknown, although they seem to be related to muscular disease, systemic inflammation, and an increase in oxidative stress, which contributes to reduced protein synthesis and accelerating protein degradation. Particularly both COPD and HF share the same type of metabolic modulation with the cellular metabolism shifting from glucose to lipid metabolism, resulting in generalized muscle dysfunction, and eventually chronic wasting and cachexia in the end stage of both diseases. Muscular atrophy contributes to muscle fatigue during exercise, which causes these patients to interrupt their exercise in spite of not exhausting their cardiac and respiratory reserves. As a result, the maximum oxygen consumption is directly related to skeletal muscle mass in both processes.

**PROBLEMS DIAGNOSIS**

The coexistence of both COPD and HF remains frequently unrecognized. The diagnosis is problematic for several reasons, especially in the elderly. Both conditions share features such as age of development, smoking as a risk factor and symptoms and signs such as exertion dyspnoea, functional disability, nocturnal cough, peripheral oedema, and jugular venous distension. However these features can be attributed to additional comorbidities, present mainly in the elderly. Therefore clinical symptoms and signs require careful interpretation, in conjunction with objective evidence of each condition. Several tests can be performed to assist in the diagnosis of each disease. A normal electrocardiogram is useful to exclude HF, nevertheless this tool lacks specificity to undoubtedly assert that diagnosis because abnormalities found frequently overlap with those seen in other conditions, including COPD. The interpretation of chest radiography maybe misleading because chest hyperinflation present in COPD patients can mask an increased cardiothoracic ratio and right ventricular enlargement can obscure left ventricular dilation. Also, whereas extra shadows commonly seen in lung disease can suggest spurious pulmonary oedema, the remodelling of pulmonary vascular bed may hide the typical alveolar pattern found in acute heart failure. Assessment of left ventricular function is mandatory for diagnosing HF. Echocardiographic acoustic windows may be impeded by air trapping in pulmonary disease, in addition in elderly patients, changes in echocardiographic parameters associated with ageing, such as reduced early diastolic filling, increased late diastolic filling, and reduced myocardial diastolic velocities, are to considered. To overcome this limitation, the use of cardiac MRI (CMRI) is currently being advocated as an alternative. Apart from providing accurate and reproducible measurements of left ventricular volumes and LVEF that are not affected by lung hyperinflation, this technique is also valuable in the correct valuation of right ventricular volume and function.

On the other hand, objective evidence of airflow obstruction is mandatory for diagnosing COPD. The presence of a post-bronchodilator FEV1/FVC < 0.70, at the spirometry, confirms the presence of persistent airflow limitation and thus of COPD. This criterion is in older patients has been repeatedly criticized for not acknowledging the age-associated physiological decline of the FEV1/FVC ratio, reaching 70% in those over 75 years of age. Therefore COPD may thus be over diagnosed in elderly patients with HF. Alternatively, an age- and sex-adjusted approach was proposed employing the lower limit of normal (LLN) of the FEV1/FVC ratio, however the superiority of the LLN over the GOLD definition has not generally been accepted. Although the GOLD guidelines acknowledge these limitations of the current definition, they still adhere to the fixed ratio for its simplicity and applicability to a broader, worldwide range of caregivers. Both the commonly used fixed ratio of FEV1/FVC as measured with spirometry, and the LLN approach bear the risk of over- and underdiagnosing true COPD, respectively. Regarding the severity of COPD, until recently it was graded on the reduction of FEV1. This approach results in overestimation of COPD severity in patients with heart failure with reduced ejection fraction, because HF itself causes a 20% reduction in FEV1. Indeed airflow obstruction is common in patients with decompensated HF contrasting with restrictive defects when HF is stable. Interstitial and alveolar oedemas cause compression and obstruction of the airways, compounded by bronchial hyperresponsiveness. With diuresis, mean FEV1 improves by up to 35% and often returns to normal. Pulmonary function tests are therefore most informative when patients are clinically euvolaemic.
For routine clinical practice, consultation of a pulmonologist would be both a pragmatic and an adequate approach. It is remarkable that, despite the importance of COPD as comorbidity in HF, the latest HF guidelines do not include spirometry among the complementary tests recommended in the management of this entity. Natriuretic peptides (NP) are very useful to reliably diagnose or rule out heart failure as the cause of acute dyspnoea in patients without COPD. Regarding COPD patients, natriuretic peptides remain accurate, at higher thresholds, in the diagnosis of HF mainly during acute exacerbation. Differently the diagnostic accuracy of BNP in patients with concurrent COPD is less certain. In patients with stable COPD and systolic dysfunction of the left ventricle or pulmonary heart, BNP levels were significantly higher compared to those of patients in whom a diagnosis of heart failure was excluded. During exacerbations, the peptide levels were found to be only modestly higher than in the clinically stable phases, nevertheless in those patients who have comorbidities such as ischemic heart disease, pulmonary embolism, arrhythmias, aortic stenosis, pulmonary hypertension and renal impairment, plasma levels of NP can be raised significantly.

An interesting study has examined the ability to identify HF in elderly COPD patients. Four natriuretic peptide assays produced comparable results in 200 stable elderly patients with a clinical diagnosis of COPD. Although each test excluded HF with reasonable accuracy (all negative predictive values above 0.85), however, the positive predictive value and overall diagnostic accuracy were lower than observed in patients with acute dyspnoea. Different cut-off values apply to COPD patients with acute dyspnoea. A single cut point for BNP to exclude/detect HF was < 100 pg/mL, with a sensitivity of 93% and a specificity of 77%.

Although not specifically tested in patients with a history of COPD, it is suggested that BNP levels > 500 pg/mL indicate acute HF in COPD. Finally, in COPD patients with BNP levels of 100-500 pg/mL, cor pulmonale (right ventricular stretch) might be the source (or moderate left ventricular failure).

In summary, very high and very low concentrations of natriuretic peptides have high positive and negative predictive values for diagnosing HF in those with both conditions.

**BETA-BLOCKERS USE IN ELDERLY PATIENTS WITH COEXISTENT COPD AND HF**

According to the ESC HF-guidelines, the HF should be treated even in COPD patients, because there is no evidence that HF should be treated differently in patients with this comorbidity. However the coexistence of both diseases creates important therapeutic dilemmas, particularly in the elderly patients. A lot of trials show the underutilization of beta-blockers in patients with CHF and coexistent COPD. In EVEREST and OPTIMIZE-HF the use of beta-blockers was ~ 65% vs 75%, and in HF-ACTION it was 88% vs 95%.

Chen et al. assessed the effectiveness of beta-blocker therapy after acute myocardial infarction in 54,962 patients, of which about 20% was affected by COPD or asthma. Patients with COPD or asthma were significantly less likely to be treated with beta-blocker therapy after myocardial infarction. Beta-blockers were prescribed only in 9,3% of patients with severe COPD or asthma. Treatment with beta-blocker was associated with a significant reduction in mortality rate over one year of follow-up also in the subgroup of patients with COPD or asthma who were not under beta-agonist therapy (RR = 0.86, 95% CI 0.73 to 1.00 p = 0.048).

Differently, in a cohort study, included 1062 patients over 65 years with COPD or asthma and concomitant coronary artery disease, over a total of 255 deaths 126 were under beta-blocker treatment. Thus, in this study beta-blocker use was not associated with any benefit on mortality.

The interaction between beta-blocker selectivity and outcome in patients with COPD and systolic left ventricle dysfunction was investigated by Mentz et al. In this study 725 patients had a history of COPD (27%). COPD patients were less likely to receive beta-blockers than patients without COPD. Among patients receiving beta-blockers, 40% received a cardioselective beta-blockers and 60% a non-cardioselective one. Treatment with beta blocker was associated with lower mortality rate among patients with COPD and in the overall population and this outcome was not affected by the selectivity of the beta-blocker used in patients with concomitant COPD and HF. Similar findings have been demonstrated in OPTIMIZE-HF.

A Cochrane meta-analysis concluded that b-1-selective b-blockers are safe: from the b-blockers currently recommended in HF therapy, only carvedilol is not
cardioselective. Metoprolol, bisoprolol and nebivolol are the best candidates in treatment of HF with comorbid COPD.

PROGNOSTIC IMPLICATIONS OF COEXISTENT COPD AND HF IN ELDERLY PATIENTS

Despite European guidelines indicating COPD as an independent predictor of worse prognosis in HF, contrasting results have been reported in HF studies regarding the impact of COPD on the prognosis. Several studies report worse outcomes in HF patients with COPD, while others have been neutral. In a study comparing the impact of different comorbidities on prognosis in 2843 patients diagnosed with HF and preserved ejection fraction and 6599 with HF and reduced ejection fraction, COPD was the only comorbidity that acted as an independent variable of mortality for both groups.

In the REPENSAR registry, the presence of airway obstruction in patients with HF did not confer a statistical excess risk of death or hospitalisations during the 2-yr follow-up period. In contrast, the presence of ventricular dysfunction in patients with COPD tended to increase the risk of mortality during the follow-up (hazard ratio 2.34, 95% CI 0.99-5.54; p<0.053). In HF-ACTION trial, COPD was associated with increased mortality/hospitalization, mortality, and cardiovascular mortality (CV)/HF hospitalization on unadjusted analysis, but not with increased mortality/CV hospitalization. Therefore the primary effect of COPD in HF patients may be increased non-cardiovascular mortality in the acute HF setting with similar outcomes following hospital discharge.

Recently, Canepa et al. performed a retrospective analysis of clinical characteristics and outcomes of the 1,533 elderly patients with HF and concurrent COPD (22%). This study reveals that COPD is an independent predictor of mortality and hospitalizations in ambulatory HF patients. Indeed, COPD carried an independent 28% increased risk of death and 19% increased risk of death or hospitalizations for cardiovascular reasons over 4 years of follow-up.

CONCLUSIONS

COPD and CHF are common diseases of the elderly that frequently coexist. COPD prevalence is dramatically rising, but reliable figures are not available because many elderly, mostly the ones plagued with disability and multimorbidity, cannot perform a good quality spirometry. Furthermore, atypical presentations contribute to conceal COPD. The combination of HF and COPD presents many diagnostic challenges mainly due to the similarities in clinical presentation and additionally due to a lack of relevant studies addressing the combination of HF and COPD. Several tests can be performed to assist in the diagnosis of each disease. Assessment of left ventricular function by transthoracic echocardiography is mandatory for diagnosing HF, while magnetic resonance imaging is the modality of choice in those with limited acoustic windows. On the other hand, objective evidence of airflow obstruction, when clinically euvoletic, is mandatory for diagnosis of COPD. Both are chronic progressive diseases and their prognosis combined is poorer than for either disease alone, therefore it is really important to recognize the coexistence of both processes early. Greater collaboration is required between cardiologists, pulmonologists, and general practitioners. Due to the high prevalence of unrecognized HF among patients with COPD, all elderly patients with persistent dyspnoea or functional intolerance despite optimal treatment for COPD should be referred to a cardiologist in order to undergo cardiac imaging to uncover potential coexistence of HF. Likewise, elderly patients with HF and persistent dyspnoea or functional intolerance despite optimal treatment should be referred to a pneumologist in order to undergo investigation including pulmonary function tests to establish or exclude coexistent COPD.

References


2 Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129-200.


innovative educational strategy on medication appropriate use and length of stay in elderly patients. Medicine (Baltimore) 2015;94:e918.


