Abstract

***Introduction*:** Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are two common, heterogeneous, long-term illnesses which cause significant morbidity and mortality. Although they both present with breathlessness, they are treated differently. Treatment of COPD focuses mainly on relieving short-term breathlessness, whilst treatment of HF has focused on long term morbidity and mortality.

***Areas covered*:** In this review, we aim to highlight the diagnostic challenges in distinguishing COPD from HF. We also explore the implications of their overlap, and the use of biomarkers and treatments for HF in patients with COPD to improve long-term outcomes.

***Expert commentary*:** Cardiovascular morbidity and mortality amongst patients with COPD is substantial. Approaches which identify patients with COPD at highest cardiovascular risk may therefore be helpful. A trial targeting those patients with COPD and raised natriuretic peptide levels might be the way to test whether cardiovascular medication has anything to offer the respiratory patient.

Keywords: COPD, heart failure, natriuretic peptides, review, therapy.

1. Introduction

The diagnosis of both heart failure (HF) and chronic obstructive pulmonary disease (COPD) is primarily clinical, based on a constellation of symptoms (mainly breathlessness during exercise and fatigue) and signs (such as peripheral oedema or raised jugular venous pressure) due to an underlying structural or functional abnormality. Distinguishing between COPD and HF can be difficult, but is important. Active treatment of chronic heart failure, when it is due to a substantial reduction in left ventricular ejection fraction (HeFREF), can approximately double a patient's life expectancy (1). However, despite a large number of trials, with thousands of patients enrolled, and enormous financial investment, there is very little evidence that treatment modifies the clinical course and mortality of either COPD or heart failure with normal ejection fraction (HeFNEF), despite some beneficial effects on symptoms (2,3).

In this review, we examine the prevalence of COPD in patients with HF and vice versa. We discuss the diagnostic challenges in distinguishing COPD from HF, suggesting that clinicians should be aware of significant overlap when assessing patients with either condition. We also explore the implications of the overlap and the possible value of using biomarkers of HF as well as using treatment of HF in patients with COPD to improve long term adverse treatment outcomes.

2. Distinguishing between HF and COPD

Exertional breathlessness is the most common presentation to a heart failure clinic. By the time patients are seen in clinic, many will have a normally contracting left ventricle on

echocardiography with a slight increase in circulating levels of natriuretic peptides, and commonly, mild abnormalities on spirometry (4). A substantial proportion either smoked or continues to smoke, many are overweight and hypertensive, and very many are elderly and treated with a cocktail of drugs, including diuretics and inhalers (4, 5). Exertional breathlessness often persists despite treatment, and attempts to clarify the medical diagnosis further are a daily item of discussion: has that patient got COPD, or HF? Is either disease present, or perhaps neither? Does the patient need follow-up, further tests, or it is appropriate to discharge him/her back to the primary care physician?

3. Epidemiology of COPD in patients with HF, and vice versa

COPD and HF share predisposing risk factors, particularly a long history of smoking and systemic inflammation, and often coexist. The reported prevalence of COPD in patients with HF varies between 10% to 50 % (6) and is higher in patients with HF who have HeFNEF, rather than HeFREF, which perhaps reflects different patient characteristics in the two conditions. Patients with HeFNEF tend to be older, are more likely to be female and to have co-morbidities. Indeed, many patients with so-called HeFNEF are misdiagnosed and many are in fact breathless due to COPD (7).

Patients with COPD have an increased risk of developing HF (8), and COPD increases morbidity and mortality in those who already have HF, with a greater burden in patients with HeFNEF, compared with those with HeFREF (9). The prevalence of HF amongst patients with COPD is around ***10-20***%, although some studies report that the prevalence might be as high as 50% (10-12). The discrepancy suggests that a high proportion of patients enrolled in

COPD registries might have undiagnosed HF (13), and it might partially explain why a substantial proportion of patients with COPD are not only treated with diuretics but also die of cardiovascular causes rather than from progressive respiratory disease (14-18).

Cardiovascular events are one of the major, if not the most common, reasons for hospital admissions in patients with COPD (19). An autopsy study found that nearly 60% of patients dying following an admission with severe COPD die of heart failure (37%) or pulmonary thromboembolism (21%), another 28% die from pneumonia, but fewer than 15% die from progression of underlying COPD (20). ***A dedicated clinical endpoint committee adjudicated the cause of death and the relationship of deaths to COPD of patients with enrolled in the TORCH (Towards a Revolution in COPD Health) study. Of the 911 deaths, the proportions attributed to COPD and to cardiovascular disease were similar (27%), and most of those attributed to cardiovascular causes were sudden (21). Subsequent reports confirmed that patients with COPD seem to be at an increased risk of sudden cardiac death, particularly when they have frequent exacerbations (14). There is some evidence that these dramatic cardiac events are more likely to be due to asystole or pulseless electric activity, rather than to ventricular tachyarrhrhythmias (22)***. Thus, the cardiovascular morbidity and mortality is substantial for patients with COPD, and might be modifiable by effective diagnosis and treatment.

4. Heart failure as a mimic of COPD

Triggered and perpetuated by chronic inflammatory responses to external pathogens (particularly smoking and air pollution), COPD is characterised by progressive narrowing of the small airways, and obliteration of the lung parenchymal tissue. The result is diminished elasticity of alveolar walls on expiration, with consequent breathlessness and fatigue

secondary to the strenuous respiratory effort made by the patients to keep the alveoli open (23, 24). A ratio of forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) of less than 70% is the diagnostic threshold for COPD (25).

Patients with HF can appear to have obstructive or restrictive respiratory pathology on spirometry similar to that observed in patients with COPD, leading to diagnostic uncertainty. More than 30 years ago, Light and colleagues observed substantial impairment in FEV1 and FVC, characteristically seen in an obstructive and restrictive lung disease, amongst 28 patients admitted with acute heart failure who were shown subsequently not to have COPD (26). The spirometric abnormalities improved once congestion was relieved. It seems that alveolar and interstitial oedema might compress airways and produce a picture similar to that observed in patients with COPD. More recently, Brenner and colleagues performed serial spirometry in patients admitted with HeFREF, and showed that apparent "COPD" resolved by 6 months in around 50% of patients once they were treated with appropriate anti-HF medication (27).

A post-hoc analysis conducted in 187 patients with both HF and COPD enrolled in the CHAMPION trial (Cardiomems Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Subjects) showed that optimising anti HF treatment and being more aggressive with diuretics in patients with invasively monitored increasing pulmonary artery pressure not only decreased the rate of hospitalisations for HF, but also for respiratory disease (28). It is possible that lowering pulmonary artery pressure with more appropriate anti HF medications causes lower rates of respiratory infections or COPD exacerbations.

Impaired lung functional tests are also seen in ambulatory patients with chronic HF who have no previous diagnosis of COPD: around 25% of patients with chronic HF have FEV1 <80% predicted, and the proportion doubles in those with more severe HF symptoms. There is thus a huge potential for misdiagnosis, leading to unnecessary prescriptions of therapies targeting the "obstructed" airways (29). Impaired lung mechanics and reduced gas diffusion are other factors that could be partially responsible of a "COPD-like" picture in patients with chronic heart failure (30, 31). Cardiomegaly and pleural or pericardial effusions can limit intra-thoracic space and consequently further reduce lung function and volumes (32). Furthermore, respiratory muscle strength is reduced in patients with HF, causing dyspnoea and exercise limitation (33). Other co-existing conditions, such as abdominal obesity, might also reduce lung volumes and function, causing symptoms erroneously attributed to COPD or HF (34). Anaemia and myocardial ischemia are other frequent comorbidities in patients with HF that might contribute to, and aggravate, breathlessness (35).

5. A common diagnostic dilemma

An imaging test demonstrating a poorly contracting left ventricle is often sufficient to establish the initial diagnosis of HeFREF (and to define the course of treatment) in a patient with shortness of breath; however, it is not so simple to make a straightforward diagnosis in patients whose left ventricle contracts relatively well (36). The prevalence of HeFNEF is reported to be on the rise, but its diagnosis remains challenging (37, 38). Several guidelines and consensus statements suggest that the presence of cardiac structural abnormalities or diastolic dysfunction on echocardiography is a requirement for the diagnosis of HeFNEF (1, 39), but not all patients with breathlessness and diastolic dysfunction on imaging have HeFNEF (40). Diastolic dysfunction is very commonly seen in older people or in patients with hypertension, who do not necessarily report breathing difficulties or have peripheral

oedema (41). Moreover, the presence of diastolic dysfunction on echocardiography does not always identify patients with a poorer outcome, particularly when natriuretic peptides are low (7, 42).

Natriuretic peptides are hormones produced by the heart. Levels rise in response to pressure or fluid overload, and result in natriuresis and vasodilation. When their plasma concentrations rise in a patient with heart failure, there is a marked increase in the risk of adverse outcome, regardless of left ventricular ejection fraction (43, 44). The updated ESC-HF guidelines suggest that an NTproBNP below 125 ng/l excludes heart failure (1). An NTproBNP level >125 ng/l, accompanied by structural heart alterations (for example, a dilated left atrium) or diastolic dysfunction, implies the diagnosis of HeFNEF in a patient with symptoms suggestive of heart failure (1). Screening using natriuretic peptides in ambulatory patients with COPD might be a strategy to confirm, or refute, the diagnosis of HF and to identify those at greater risk of adverse outcome (table 1); such a strategy differentiates well between patients with lung and heart problems amongst those who present acutely with shortness of breath (45,46).

The difficulties experienced by cardiologists in diagnosing heart failure are encountered in a similar manner by respiratory physicians when they attempt to separate normal from abnormal lung function tests. There is no equivalent of natriuretic peptides to help in the diagnosis of COPD. Adult smokers commonly have respiratory symptoms which limit their physical activity. They also have a substantial number of exacerbations requiring antibiotics and/or steroids, and evidence of chronic bronchitis on computed tomography (CT) scans even when spirometry is normal (FEV1/FVC$\geq$70), suggesting that spirometry may not be an adequate screening tool for COPD (47, 48). As a consequence of their symptoms, many

patients with normal spirometry are treated with inhaled bronchodilator therapy despite not fulfilling clear diagnostic criteria for COPD. Such treatment might have a deleterious impact on any underlying heart disease, as we will discuss later.

In the elderly, a decline in FEV1/FVC ratio <0.70 can be a physiological finding not related to obstructive lung disease, and other measurements have been proposed with the aim of avoiding over-diagnosing (and again, over-treating) COPD (49, 50). However, impaired lung function tests in an elderly individual are not necessarily a benign finding (51), particularly with worse spirometry and particularly when NTproBNP is increased. In a study of 3242 men drawn from the general population, without prior myocardial infarction or HF, and aged 60–79 years, around 30% had FEV1/FVC<0.7. Those with a poorer predicted % FEV1 had more biochemical evidence of inflammation (raised C-reactive protein (CRP)) and cardiac damage (raised troponin I and NTproBNP) than those with a normal FEV1. The presence of moderate, or severe (FEV1/FVC <0.70 and FEV1 <80%) airflow obstruction was associated with a high risk of developing HF, and % predicted FEV1 was an independent predictor of incident HF even in models corrected for NTproBNP (52). Decreasing FEV1 was one of the strongest predictors of incident HF in a study of around 6000 individuals older than 65 years, with and without known ischemic heart disease. (53).

Right ventricular dysfunction and raised pulmonary artery pressure, as frequently occur in patients with COPD, are common clinical findings shared by patients with COPD and HF and might contribute to an increase in NTproBNP (and other plasma biomarkers) even in those with no left ventricular systolic dysfunction (54-57). It is not surprising that raised pulmonary artery pressure, and NTproBNP levels, carry powerful prognostic information in both populations (58,59).

6. Issues associated with treating heart failure in patients with COPD

Beta-blockers are currently prescribed to around 90% of patients with HeFREF. The commonest reason not to prescribe a beta-blocker is the concomitant presence of respiratory disease (60, 61). The concern is that beta-blockers might have deleterious effects on lung function, such as bronchoconstriction, and might increase the airway responsiveness of patients with COPD (62).

Despite their beneficial effect on left ventricular size and function, and on long term outcome, in patients with HeFREF (63), beta-blockers can decrease FEV1 and worsen airway resistance. The tolerability (defined as reaching, and maintaining, guideline-recommended target doses after 12 weeks treatment) of two widely used beta-blockers (carvedilol and bisoprolol) was assessed 883 elderly patients with HF in the Cardiac Insufficiency Bisoprolol Study in Elderly (CIBIS-ELD). Patients were naïve to, or not taking an adequate dose of, beta-blocker. Only 7% of the patients enrolled had a previous diagnosis of COPD; 31% of patients reached target doses of treatment with beta-blockers, and there was no difference in the tolerability of the two beta-blockers. Both beta-blockers improved clinical endpoints such as LVEF, and 6 minute walk test distance (+19 m for bisoprolol and + 13 m for carvedilol) after 12 weeks of treatment, but they had a differential effect on FEV1: FEV1 was unchanged by the cardioselective bisoprolol but significantly worsened in those treated with the non-selective carvedilol. There was a greater number of pulmonary adverse events with carvedilol than bisoprolol, although the number of events was modest (44 (10%) vs 16 (4%), respectively, p=0.01) (64).

In patients with HF and co-existing moderate or severe COPD, bisoprolol, but not placebo, caused a substantial decrease in FEV1 (–70 mL from baseline vs +120 mL in the placebo group, p=0.01) but without significantly affecting symptoms or quality of life (65).

In a cross-over trial in 51 patients with HF (mean LVEF 37%) of whom 35% had COPD, the respiratory, haemodynamic and biochemical effects of three licensed beta-blockers for patients with HF (metoprolol, carvedilol and bisoprolol) were evaluated. Compared to metoprolol and bisoprolol, carvedilol not only decreased FEV1, but also plasma NTproBNP, suggesting that it might have a more beneficial effect on the underlying heart failure. There were no major differences between the beta blockers in six-minute walk test (66).

Despite the frequently given advice to avoid β blockers in people with COPD, cohort meta-analyses suggest that patients with COPD but no clinically apparent heart disease might have a *better* prognosis when they are prescribed beta-blockers, and might have a lower risk of experiencing a COPD exacerbation; this is probably because many of them had had a diagnosis of underlying cardiovascular disease, including ischemic heart disease or heart failure, the likely reason for which a beta-blocker was originally prescribed (67-69). Similarly, large studies suggest that the use of other widely used anti-HF medications (such as ACE-inhibitors, or angiotensin II receptor blockers) in patients with COPD is associated with lower mortality, perhaps reflecting better diagnosis and treatment of relevant comorbidities (70, 71).

7. Issues associated with treating COPD in patients with heart failure

Various treatments prescribed for COPD, alone or in combination, acutely improve lung function and symptoms, and might also have beneficial effect on cardiac haemodynamics (such as increasing the cardiac index, or lowering the end-diastolic ventricular pressure, and/or peripheral resistance) in patients with HF (72, 73). The long term prescription of treatments for COPD has never been convincingly shown to reduce mortality (74-76). Worse, some of these treatments might even be harmful for patients with COPD, particularly in those with underlying heart disease. Au and colleagues reported that, amongst 1529 patients with HeFREF, the use of inhaled beta-agonists was associated with an increased risk of HF hospitalizations or death, with a dose-response relation (77, 78). Some bronchodilatators increase the risk of all-cause mortality and cardiovascular death in patients with respiratory disease (79). Anticholinergic drugs, in particular tiotropium (80, 81), have recently been associated with an increased risk of death, due to possible pro-ischaemic and pro-arrhythmic effects (82, 83). ***The chronic and indiscriminate use of inhaled steroids further exposes patients to the risk of pneumonia or incident (or worsening) diabetes (84). Identifying patients in whom discontinuation of unnecessary COPD therapy is safe has to be encouraged (85).***

8. Expert commentary

Heart failure and COPD have many things in common. They share a similar clinical presentation and an increasing prevalence (86, 87). They also share a poor prognosis, and a high social and economic burden.

As is the case for heart failure, COPD is a heterogeneous disease, and different phenotypes of patient have just started to be identified: they might have different characteristics and outcome, not all of which might necessarily benefit from similar treatment strategies.

One example is that it is popularly thought that COPD progresses as a consequence of a rapid decline in FEV1. However, a substantial proportion of patients have COPD with a reduction in FEV1, but their FEV1 then declines at an approximately normal age-related rate. Such patients have a decreased FEV1 in their early adulthood (88), perhaps as a consequence of an exposure to one or another environmental factor, or because of some genetic predisposition. A therapeutic approach targeted at preventing rapid decline in FEV1 would be inappropriate for such patients.

Moreover, other different subsets of individuals with COPD might exist. Those who have more cardiovascular comorbidities and evidence of inflammation have the highest mortality (usually cardiovascular); whilst those with lowest FEV1 and severe emphysema are at greatest risk of exacerbations and COPD admissions. In contrast, those with only mild symptoms have a low risk of exacerbations, and a 3 year mortality rate of only 3% (89).

The wider use of biomarkers, such as natriuretic peptides, has enabled cardiologists to identify individuals with HF at low or high risk of adverse outcome, which may help in targeting specific treatments (7, 90), such as mineralcorticoid receptor antagonists (MRA). Currently, raised levels of NTproBNP are a mandatory criterion for enrolment in trials in HeFNEF. It may be that natriuretic peptides could be used to identify patients with COPD at greatest cardiovascular risk, likely to benefit from treatments targeted at heart disease (91). As with diabetes, where treatment that reduces cardiovascular risk, rather than treatment

aimed at reducing blood sugar, improves prognosis (92, 93), targeting cardiovascular risk in patients with COPD (rather than targeting lung function) might have a similar effect.

An example might be the use of statin in COPD. However, although several large observational studies have suggested that statins might have beneficial effects in patients with COPD (70, 71), the STATCOPE trial of simvastatin in 885 patients with COPD without overt cardiovascular disease or diabetes was stopped for futility after a median follow up of 641 days (94). Another multicentre trial investigating the effect of metoprolol on the incidence of acute exacerbations in patients with moderate-severe COPD is ongoing (95).

Markers of systemic inflammation, such as fibrinogen, might further provide insight into COPD pathophysiology and suggest other therapeutic options in other subsets of patients (96). Biomarkers might also be a useful tool to describe the heterogeneity of COPD exacerbations, which might be due to different pathogens, with different inflammatory responses, that might be prevented, or treated, in different ways (97).

9. Five-year view

Whilst trials in heart failure have focused on the effects of treatments on the rate of hospitalisations, and importantly, mortality, trials in COPD trials have mainly assessed the effects of interventions on quality of life and symptomatic relief. Closer collaboration between cardiologists and lung specialists might be helpful as the diseases overlap and are sometimes not easily distinguishable; sharing the experience gained by cardiologists in recent decades might help improve trial design for patients who have COPD, either alone or with concomitant, ***and often undiagnosed***, HF.

10. Conclusions

COPD and HF are heterogeneous, and frequently overlapping, diseases. The development of pharmacotherapy for COPD has been intense, but has been mainly limited to compounds targeting airways obstruction, with no evidence of a mortality benefit, in contrast to the results of many trials in patients with HF. Death amongst patients with COPD is most commonly from cardiovascular causes, and thus approaches which identify patients with COPD at highest cardiovascular risk may be helpful. A trial targeting those patients with COPD and raised natriuretic peptide levels might be the way to test whether cardiovascular medication (beta-blockers, ACE-inhibitors or MRA) has anything to offer the respiratory physician.

Key issues

- Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are two common and heterogeneous diseases that share a similar clinical presentation and might coexist; distinguish between the two is essential.

- Identifying and treating patients with heart failure and reduced left ventricular ejection fraction (HeFREF) substantially prolongs patient's life expectancy, whilst there is very little evidence that treatment modifies the clinical course and mortality of either COPD or heart failure with normal ejection fraction (HeFNEF).

- As in heart failure, and many other clinical conditions, raised natriuretic peptides identify patients with COPD at higher cardiovascular morbidity and mortality risk.

- Trials targeting cardiovascular risk in patients with COPD might be the way to test whether cardiovascular medication improves the long term outcome of these patients.

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Study	Patients	Diagnostic criteria for COPD.	Natriuretic peptides plasma levels	Outcome
Inoue (98)	60, without known cancer, cardiac or renal medical history.	GOLD criteria	Mean BNP: 41.0+6.6 pg/ml (vs 14.8+2.7 pg/ml in controls). BNP plasma levels increased with increasing COPD severity.	BNP correlated with non-invasive estimation of pulmonary artery systolic pressure and LVEF. Only two patients died during 3 year follow-up.
Kanat (91)	37 with a COPD exacerbation without evidence of cor pulmonale or heart failure; 15 controls with stable COPD.	GOLD criteria	BNP was elevated in 30 patients with acute COPD (81%). Patients with elevated BNP were randomised to mild diuretic (triamterene 50 mg + hydrochlorothiazide 25 mg/day) vs no diuretic. Median BNP: Randomised to mild diuretic: 742 (283-3228) pg/ml Randomised to no-diuretic: 405 (184-2108) pg/ml Controls: 101 (63-342) pg/ml	Adding mild diuretic to standard treatment of COPD rapidly reduces BNP levels.
Van Gestel (99)	261 with LVEF>40% undergoing major vascular surgery (AAA, CEA or LLR). 144 had COPD.	GOLD criteria	73% of those with elevated NTproBNP (defined as >500 pg/ml) had COPD, whilst only 52% of those with not elevated NTproBNP had COPD. Median NTproBNP: 125 pg/ml no COPD 212 pg/ml mild COPD 170 pg/ml moderate COPD 352 pg/ml severe COPD	23 patients during 1 year follow-up. NTproBNP was independent predictor of mortality in all patients as well as in those with COPD. The 1 year survival rate in patients with COPD and NTproBNP<500 pg/ml was 88% vs 65% in those > 500 pg/ml (<0.01).
Leuchte (100)	176 with various pulmonary disease (of whom 45 had COPD) undergoing RHC.	An impaired lung function test supported by radiographic and immunologic or histopathologic findings (depending on the disease).	Mean BNP was 297 (54) pg/ml in patients with mean PAP>35 mmHg vs 26 (4) in those with mean PAP<35 mmHg.	BNP and mean PAP>35 mmHg were the strongest predictors of mortality.

Waschki (101)	170 with COPD without clinical signs of HF.	GOLD criteria	Median NTproBNP was higher in nonsurvivors (98 (49-209)pg/ml vs 64 (38-106) pg/ml, p=0.038	NTproBNP was not an independent predictor of mortality.
Stamm (102)	796 smokers without IHD, HF or CKD.	GOLD criteria	Median NTproBNP was 49 (22-94) pg/ml. Median NTproBNP in nonsurvivors was 71 (36-107) pg/ml vs 47 (21-93) in survivors.	An NTproBNP above the median was an independent predictor of mortality (HR = 2.19, 95% CI 1.07–4.46, p = 0.031).
Wannamethee (52)	3242 men without MI or HF	GOLD criteria. Data presented in 5 groups, based on predicted FEV1.	NTproBNP (median, pg/ml): <5th percentile of predicted FEV1: 116 (55-257) 6-24th: 109 (49-220) 25-49th: 87 (44-160) 50-74th:78 (38-147) >75th: 81 (41-146)	Reduced FEV1 and moderate or severe (FEV1/FVC <0.70 and FEV1 <80%) airflow obstruction was independently associated with incident HF. Associations between FEV1 and incident HF remained after adjustment for NTproBNP and cTNT.

Table 1. Summary of studies investigating the potential role of natriuretic peptides in patients with pulmonary diseases. Abbreviations used: AAA - abdominal aortic surgery; CEA - carotid endarterectomy ; LLR - lower limb arterial reconstruction; GOLD - Global Initiative for Chronic Obstructive Lung Disease; BNP - B-type natriuretic peptide; NTproBNP - N-terminal prohormone of brain natriuretic peptide; LVEF - left ventricular ejection fraction; FU - follow up; COPD - chronic obstructive pulmonary disease; RHC - right heart catheterization; PAP - pulmonary artery pressure; MI - myocardial infarction; IHD - ischaemic heart disease; HF - heart failure; CKD - chronic kidney disease; FEV1 - forced expiratory volume in one second; cTNT - cardiac troponin T; HR - hazard ratio; CI - confidence interval.