Chronic Obstructive Pulmonary Disease and Heart Failure: A Breathless Conspiracy

Short title:- COPD in Heart Failure

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Conflict of interest: none declared.

Synopsis

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are both common causes of breathlessness and often conspire to confound accurate diagnosis and optimal therapy. Risk factors (such as aging, smoking and obesity) and clinical presentation (for instance, cough and breathlessness on exertion) can be very similar, but the treatment and prognostic implications are very different. In this review, we discuss the diagnostic challenges in individuals with exertional dyspnoea. We also highlight the prevalence, clinical relevance and therapeutic implications of a concurrent diagnosis of COPD and heart failure.

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

Key Points:

- COPD and heart failure are both common and share many risk factors
- Heart failure and COPD frequently co-exist and such patients have a poor prognosis
- Determining whether breathlessness is due predominantly to lung or heart disease can be difficult; missed diagnoses are common
- The combined effect of treatments for HFrEF on outcome is large and therefore the diagnosis should not be missed
- COPD may deter the introduction or dose of beta-blockers, a key treatment for HFrEF
- Treatments do not substantially alter outcomes for COPD or HFpEF

Introduction

Heart failure (HF) and chronic obstructive pulmonary disease (COPD) are increasingly common and often co-exist. Together they probably cause or complicate about 10% of all hospital admissions. However, perhaps fewer than half of patients who have these conditions have appropriate investigation and diagnosis. Furthermore, the diagnosis of one condition may obscure the presence of the other (1, 2). HF and COPD have much in common, including risk factors (for instance, a lifelong history of smoking and obesity), symptoms (breathlessness and cough) and clinical signs (lung crackles and peripheral oedema). Differentiating between the two conditions is a diagnostic challenge, but their correct identification is essential: the correct treatment will improve the long-term outcome of many patients with heart failure, whereas there is little treatment that has a profound impact on outcome for COPD (3, 4).

In this review, we will discuss the diagnostic challenges in distinguishing COPD from chronic heart failure in patients with exertional dyspnoea. We will also discuss the prevalence, clinical relevance and therapeutic implications associated with a concurrent diagnosis of COPD and heart failure.

COPD and heart failure: a diagnostic challenge

Clinical history and physical examination

An accurate clinical history usually leaves more doubts than certainties in a breathlessness patient, as signs and symptoms are not specific for either condition. Advanced age increases the risk of having both COPD and HF. Many of those who report dyspnoea on exercise are or have been smokers, many are obese and many have coronary artery disease. Cough is frequent, and can be due to COPD, heart failure or use of angiotensin-converting-enzyme inhibitors (ACE-I). Clinical signs of air flow limitation (such as wheeze) or high cardiac filling pressure (such as lung crackles, or raised jugular vein pressure) lack specificity and are common only when disease is severe (5,6). Non-intentional weight loss, malnutrition, and cachexia are also common in the more advanced stages of either COPD or HF (7, 8).

Chest-x ray and other radiological findings

A normal chest X-ray does not rule out a diagnosis of COPD or chronic HF (9). Abnormal findings are non-specific except, perhaps, when there is frank pulmonary oedema. However, other causes of cough and exertional breathlessness can be diagnosed on a chest X-ray, such as lung cancer, tuberculosis and pulmonary fibrosis. An X-ray should always be considered.

Electrocardiography

A normal ECG excludes heart failure for practical purposes, but not COPD (10). Although many subtle ECG changes have been reported in patients with COPD, their clinical relevance has not been demonstrated (11). Prompt identification of atrial fibrillation, a common ECG finding in both conditions, is important as anti-coagulation is usually indicated to prevent stroke.

Spirometry

A ratio of forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) of less than 70% after administration of a bronchodilator is the key diagnostic criterion for COPD (12). This definition seems quite straightforward, but spirometry can be easily misinterpreted, leading to inappropriate diagnosis and treatment (13). Up to 25% of patients who meet the spirometric criterion for COPD will have a result within the normal range on repeat testing without receiving any treatment that could explain the difference (14, 15). On the other hand, a substantial proportion of current, or past, smokers with respiratory symptoms, apparent exacerbations, and exercise limitation has evidence of airway disease on computed tomography scans, despite normal spirometry (16). The FEV1/FVC ratio also declines with age and heart failure may cause further reductions.

Biomarkers

With rare exceptions (such as constrictive pericarditis), when intra-cardiac pressures rise or renal water and salt retention occur leading to fluid overload, the heart produces natriuretic peptides (NPs) as a counter-regulatory strategy designed to cause natriuresis and vasodilation. Increasing plasma concentrations of NPs are the single most powerful predictor of adverse outcome in patients with heart failure, regardless of left ventricular ejection fraction (17, 18). A normal plasma concentration of NPs rules out serious cardiac dysfunction (in constrictive pericarditis, plasma concentrations of NPs are lower than expected from the clinical picture but rarely normal). The diagnostic utility of NPs is currently recognised by all international guidelines on heart failure, including the National Institute for Health and Care Excellence and the European Society for Cardiology, to rule out important cardiac dysfunction in patients with suspected HF, acute or chronic (3).

Screening studies suggest that up to 50% of patients with COPD have increased plasma concentrations of NPs, although no large definitive study exists (table 1)[19-22]. Raised plasma NPs in patients with COPD predict a higher mortality, whether or not they have received a diagnosis of HF (23, 24). For patients with COPD, increased plasma concentrations of high-sensitivity troponin-I, suggesting ongoing myocardial damage, are also associated with high rates of CV events, but not with exacerbations of COPD (25). No blood biomarkers are currently recommended for the identification of people with COPD. Patients with an elevated plasma concentration of NP should be investigated further, usually by echocardiography.

Echocardiography

Cardiac imaging (most commonly echocardiography) is an essential investigation for breathless patients who have an elevated plasma NP or in whom a cardiac contribution to breathlessness is suspected or needs to be excluded. It is important not to miss patients with a reduced left ventricular ejection fraction or severe valve disease, for which highly effective treatments exist. If these abnormalities are excluded, a dilated left atrium implies that the patient has abnormal left ventricular diastolic function and suggests the diagnosis of HFpEF. An echocardiogram should be considered in patients with an exacerbation of COPD, as around 25% of patients will have an important, potentially treatable, underlying heart problem (26, 27).

How common are COPD and heart failure?

Everyone gets breathless with sufficient exertion. Breathlessness precipitated by modest levels of exertion that a healthy young person can easily manage is very common, but is frequently not reported or investigated. Many subjects, or sometimes their doctors, attribute exertional dyspnoea to simply “getting older” or “being unfit or fat”. Consequently, many cases of heart failure and/or COPD are not diagnosed until symptoms or signs become severe enough to require a hospital admission. Use of a loop diuretic is also common in primary care as treatment for exertional dyspnoea or ankle swelling: its use might temporarily mask symptoms of heart failure. Initiation of loop diuretics should prompt further investigation of cardiac function (28). Robust, objective criteria to identify, or rule out, cardiac or lung disease as a cause of breathlessness are, with the exception of NPs, lacking. Thus, the reported prevalence of COPD and HF varies substantially, depending on the characteristics of the population studied, the context and period of time in which data were collected, the geographic area and exposure to different environmental risk factors and, most importantly, the diagnostic criteria used to define HF and COPD.

At least 5% of the adult population is said to have COPD, whilst the prevalence of heart failure is perhaps 1-2%. Many reports suggest that a large proportion of breathlessness patients have both conditions (tables 2[26, 29-36] and 3[37-48]). It's worth noting that the diagnosis of "heart failure" includes those with either a reduced (HFrEF) or preserved (HFpEF) left ventricular ejection fraction on imaging, which have a similar prevalence.

Prevalence and prognostic relevance of HF in people with COPD

In surveys of COPD, heart failure is usually reported in <20% of patients (table 2). Despite the high prevalence of ischaemic heart disease, smoking, and echocardiographic abnormalities in patients with COPD, COPD itself is, surprisingly, not strongly associated with heart failure in epidemiological studies. Perhaps once a diagnosis of COPD is made, clinicians do not look for other problems to explain symptoms. However, missing a diagnosis of heart failure may have important consequences. In a cohort of 404 patients aged >65 years with COPD diagnosed in primary care, a detailed cardiovascular examination identified previously undiagnosed heart failure in 21%, of whom about 50% had HFpEF and 50% HFrEF (35). A diagnosis of HF approximately doubled the risk of mortality in models adjusted for age and other comorbidities. Of those with COPD who were thought not to have HF, 22% were treated with a diuretic, and ~1/3 had an NT-proBNP >125 ng/l, suggesting that many of these patients also had heart failure.

Amongst 1,664 ambulatory patients with COPD enrolled in a multicentre registry in Spain and the USA (BODE), the prevalence of self-reported HF, supported by review of medical records, was ~16%, which was associated with a 33% increase in mortality (29). A recent analysis of electronic health records from Sweden, which included data from primary and secondary care on ~90,000 patients aged≥ 35 years, showed that, compared to those with COPD alone (n=885, 1%), those who had HF as a coded co-diagnosis (n=99, 10%) had a 7-fold higher mortality (36).

Prevalence and prognostic relevance of COPD in people with HF

The prevalence of COPD amongst patients with HF ranges from 10-20% in large trials and registries where COPD was either self-reported by patients or based on the opinion (non-standardized) of researchers (table 3). In smaller studies that used lung function tests to evaluate airflow obstruction objectively, up to 50% of patients with HF have abnormal spirometry. This wide discrepancy might suggest that the diagnosis of COPD is often missed, *perhaps* because cardiologists pay little attention to airway disease in the presence of a more deadly, but treatable, condition. However, it is also possible that HF has effects on the lung that mimic the effects of COPD leading to over-diagnosis. Interstitial lung oedema can compress alveoli and distal airways; cardiomegaly or pleural effusion can reduce the intrathoracic space and compress lung volumes; decreased respiratory muscle strength can reduce inspiratory and expiratory forces; frailty may impair the ability to perform spirometry accurately and normal values in those aged >80 years of age are not well-defined, which might lead to over-diagnosis by spirometry (49). Moreover, effective treatment for heart failure can normalise spirometry and reduce hospitalisations for respiratory infection (50, 51). Interpreting spirometric data in a patient with poorly controlled heart failure can be difficult.

In contrast to the clear increase in mortality associated with a diagnosis of heart failure in patients with COPD, it is less clear what the implications of an additional diagnosis of COPD is for patients with HF. In a cohort of nearly 5,000 patients referred between 2000-2016 to a single out-patient clinic with suspected HF in the UK who underwent comprehensive evaluation by echocardiography, natriuretic peptides and spirometry, a diagnosis of COPD, defined as $FEV_1/FVC<0.7$, was only weakly, and not independently, associated with an increased risk of death amongst patients with HFrEF, and not at all in those with HFpEF (44). Using anonymised electronic records from >50,000 patients with incident HF in primary care in the UK, Lawson and colleagues found that COPD was only associated with an increased risk of death and/or hospitalisations in the most severe cases, with the risk increasing progressively with the use of triple inhaler therapy, the need for oral steroids and the use of long term home oxygen (52).

Recent data from the European Society of Cardiology Heart Failure Long-Term Registry, which enrolled >16,000 patients with heart failure across 211 centres in Europe over a period of 24 months, suggest that COPD increases the risk of cardiovascular mortality (but not all-cause mortality) and re-admissions, particularly due to worsening heart failure, over the following 12 months (39). Similar results were reported in an analysis of the **S**ystolic **H**eart failure treatment With the **I**$_f$ Inhibitor ivabradine **T**rial (SHIFT). The composite of cardiovascular deaths or heart failure hospitalisations occurred more often in patients with both HF and COPD, rather than HF alone, but no difference in mortality was observed (41). Whether these associations are related to COPD itself (which might predispose to frequent respiratory infections or arrhythmias, leading to HF admissions) or to other factors (such as a lower use of HF medications in patients with concurrent COPD and HFrEF) is not clear (53-55).

Therapeutic concerns

Beta-blockers improve the long-term prognosis of patients with HF due to left ventricular systolic dysfunction (3, 56). However, concerns about the potential for beta-blockers to cause bronchoconstriction and block the effect of sympathomimetic bronchodilators dissuades many from giving these agents in adequate doses, if at all, to patients with concomitant heart failure and COPD (table 3). However, the available clinical evidence suggests that these fears are unfounded. Small randomised trials show that any decline in FEV1 associated with beta-blockers does not translate into worsening symptoms or quality of life in patients with HF and COPD (57, 58). The use of a cardio selective beta-blocker, such as bisoprolol or nebivolol, might be preferred, at least theoretically, when there is concern about tolerability (59, 60).

Perhaps surprisingly, there is accumulating evidence from observational studies and sub-analyses from randomised trials conducted in patients with COPD which suggest that a higher heart rate is associated with an increase in mortality, and that beta-blockers might reduce exacerbations of COPD and prolong survival (61-63). Some of this apparent benefit might reflect inadvertent, “accidental” treatment of undiagnosed heart failure. A multicenter, prospective, randomized, double-blind, placebo-controlled trial is currently ongoing to test whether metoprolol reduces time to first exacerbation of COPD and of cardiovascular events in patients with moderate to severe COPD (ClinicalTrials.gov Identifier: NCT02587351) (64).

There is no evidence that treatment for COPD improves long-term survival substantially. Beta-agonists can improve lung function tests in patients with COPD, but they might worsen cardiovascular and HF outcomes, especially for patients with HFrEF who are not protected by beta-blockers (65-67). Inhaled steroids may increase the risk of pneumonia (68). Oral steroids may increase sodium and water retention (69). Certainly, a large proportion of patients with COPD can tolerate de-escalation of respiratory therapies, particularly those at low risk of exacerbations. Attempts to identify patients in whom treatments for COPD can be discontinued should be encouraged (70, 71).

Conclusions

Neither COPD nor HF has a robust definition, creating uncertainty about the true prevalence of either condition. Missed diagnoses are common especially when one or other condition provides a seemingly adequate explanation for a patient’s symptoms. However, there is no doubt that these two conditions commonly co-exist.

For patients with COPD, no specific treatment improves survival but they have high rates of cardiovascular events, and often die of the consequences. Greater focus on cardiovascular rather than respiratory disease in patients with COPD might improve outcomes. However, there is no doubt that appropriate treatment reduces the morbidity and mortality of patients with HFrEF, with or without co-existing COPD.

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Study	Year	N	Age -Y	Men-%	COPD diagnosis	HF-%	Diuretic-%	Oedema -%	Current Smoker -%	IHD -%	AF-&	Creatinine	Abnormal NPs - %	Criteria used to diagnose HF and prevalence
Cross-sectional[19]	2001-2003	200	73	58	Clinical or GOLD (59%)	0	22	19	NR	34	9	90 µmol/L	~50	ESC criteria: 26% (15% HFrEF).
Cross-sectional[20]	2006	170	64	75	GOLD	Excl.	NR	Excl.	42	NR	NR	NR	23	Echocardiography: 3% had LVEF ≤50%
Prospective, observational[21]	2004-2008	140	67	46	GOLD	NR	27	19	82	NR	9	92 µmol/L	>50	Echocardiography: 11% had LVEF <45%.
Prospective, observational[22]	NR	218	70	76	GOLD	0	22	19	24	17	NR	5% CKD	>50	Echocardiography: 14% HFrEF

Table 1: Screening by natriuretic peptides (NPs) in patients with chronic obstructive pulmonary disease (COPD; only studies with >100 patients). Abnormal NPs includes NT-proBNP >125 ng/l or BNP >35 ng/L. Abbreviations used: N- number of patients; HF – heart failure; HFrEF – heart failure with reduced left ventricular ejection fraction; NR – not reported; Excl = excluded; IHD – ischaemic heart disease; AF – atrial fibrillation; CKD – chronic kidney disease.

Prevalence and clinical relevance of heart failure in patients with COPD

Study	Size	Year	Country	COPD population and definition	HF definition	Prevalence of HF	CV Therapies in patients with COPD		Outcome findings
Divo[29]	1,664	1997-2009	USA and Spain	Ambulatory, GOLD (≥3: 56%)	Self-reported/ medical records	16%	NR		HF increased risk of death (HR: 1.33 (95%CI: 1.06–1.68); p= 0.02)
Cazzola[30]	341,329	2006	Italy	Primary care; ICD-9.	ICD-9	8%	NR		NR
Curkendall[31]	11,493	1997-2000	Canada	Gov. database; ICD-9 & prescribed inhaler	ICD-9	19%	Diuretics: 57%; Digoxin: 17% BB: 10%; ACE-I: 34%		Patients diagnosed and treated with COPD are at high risk for CV morbidity and mortality.
Holguin[32]	~47 million	1979-2001	USA	Hospital Discharge; ICD-9	ICD-9	10%	NR		Compared to those without COPD, in-hospital mortality for HF is higher in patients with COPD.
McCullough[33]	417	1999-2000	USA/Europe	Emergency department (dyspnoea); self-reported	Framingham and NHANES criteria	21%	HF: Diuretic 53% Digoxin: 35% ACE-I:37%; BB: 21%	No HF: Diuretic: 25% Digoxin: 6% ACE-I:19%; BB: 7%	The emergency physician identified only 37% of HF cases. Patients with HF had higher BNP (mean 587 pg/mL) than those without (108 pg/mL).
Freixa[26]	342	2004-06	Spain	First COPD admission: ATS/ERS criteria	Self-reported + Echo 3 months after discharge	13% LVSD (9% unknown) 14 DD ≥grade 3 (10% unknown)	NR		NR
Spece[34]	2,391	2005-11	USA	Hospital Discharge; ICD-9	ICD-9	23%	NR		CV causes are common reasons for readmission.
Boudestein[35]	404	2001-03	Nederland	Primary care, clinically diagnosed	ESC criteria	21% (previously undiagnosed; 50% had HFpEF)	HF & COPD Diuretic 34% ACE-I/ARB:35% BB: 16%	COPD only Diuretic: 22% ACE-I/ARB:22% BB: 11%	Newly diagnosed HF was independent predictor of mortality (HR: 2.1; 95% CI: 1.2–3.6; P= 0.01).
Kaszuba[36]	984 (~3%)	2007	Sweden	Primary and secondary care;	ICD-10 codes	10%	NR		In univariate analysis, mortality in patients with COPD and

				ICD-10				coexisting heart failure was 7 times higher than in those with COPD alone.

Table 2: prevalence of heart failure in patients with COPD. Abbreviations used: BB – beta-blockers; LVEF – left ventricular ejection fraction; HFpEF – heart failure with preserved LVEF; HFrEF – heart failure with reduced LVEF; CV – cardiovascular; LVSD – left ventricular systolic dysfunction; ERS - European Respiratory Society; ATS - American Thoracic Society; ICD - International Classification of Diseases.

Prevalence and clinical relevance of COPD in patients with heart failure									
COPD adjudicated by clinical notes/clinical evidence/past medical history/therapy for COPD									
Study	Prevalence of COPD	Size	Year	Country	HF population/ diagnosis	Treatment for Heart Failure			Outcome
						BB (COPD vs no COPD)	ACE-i/ARB (COPD vs no COPD)	Diuretic (COPD vs no COPD)	
De Blois[37]	17%	4132	2000-2008	Norway	Mixed, >80% HFrEF; ESC guidelines	74% vs 84% (p<0.001)	Similar: ~90%	90 vs 86% (p=0.002)	COPD independently predicted death (HR, 1.19; 95% CI, 1.02 to 1.39; p=0.03)
Mentz[38]	10%	4133	2003-2006	USA, Europe, SA	Acute/ LVEF≤40%	63% vs 71% (p=0.001)	80 vs 85% (p=0.01)	Similar: ~97%	COPD was associated with ACM and CV death/HFH only in univariable analysis
Canepa[39]	19% AHF 14% CHF	16,329	2011-2013	Europe	Mixed, ~70% HFrEF. IV therapy for AHF	CHF: 77 vs 85% (p<0.001) AHF:51 vs 56% (p<0.001)	CHF: ~85%, similar AHF: 64%, similar	CHF:88 vs 78%;p<0.001) AHF: 73 vs 62 %; p<0.001)	Greater in-hospital mortality in those with COPD (8% vs 5%). COPD was not independent predictor of ACM, but predicted HFH.
Canepa[40]	22%	6,975	2002-2005	Italy	Chronic, ~90% HFrEF/LVEF<40% or HFH in previous 12m	44% vs 71% (p<0.001)	91% vs 94% (p<0.0001)	93% vs 89% (p<0.001)	COPD was an independent predictor of ACM (HR 1.28, 95% CI 1.15-1.43, p < 0.0001) and hospitalisations
Tavazzi[41]	11%	6,505	2006-2009	37 Countries	Chronic, HFrEF/LVEF<35%, SR and HFH in prior 12 months	69% vs 92% (p<0.001)	ACE-I: Similar (~79%)	89% vs 82% (p<0.001)	The primary endpoint (CV death or HHF), but not ACM, was more frequent in patients with COPD.
Parissis[42]	25%	4,953	2006-2007	9 Countries	Acute, >50% HFrEF/ ESC guidelines	21 vs 24% (p=0.055)	ACE-I: 34 vs 31% (p=0.042) ARB: 26 vs 28 (ns)	35 vs 31% (p=0.006)	Similar in-hospital mortality (~10%).
Mentz[43]	25%	20,118	2003-2004	USA	Acute, HFrEF/LVSD at admission	52 vs 57% (p<0.001)	Similar (54%)	LD: 69 vs 61% (p<0.001)	COPD increased in-hospital non CV mortality, but not

									post-discharge mortality.
COPD diagnosed by spirometry									
Cuthbert[44]	50%	3,514	2000-2016	UK	Chronic at first visit, ~25% HFpEF/reduced LVEF or NT-proBNP>400 ng/l	54% vs 62%	Similar: 71% vs 72%	LD: Similar: 72% vs 70%	COPD weakly associated with ACM in HFrEF, but not HFpEF.
Jacob[45]	26%	8,099	2009-2012	Spain	Acute, 38% HFrEF/clinical and radiological	Admission:30% vs 45% (p<0.001)	Admission: Similar (~56%)	LD: 75% vs 68% (p<0.001)	COPD only associated with readmissions at 30 days.
Iversen[46]	35% (vs 22% self-reported)	532	2001-2004	Denmark	Acute, 42% HFpEF/requiring IV diuretic	17% vs 32% (p=0.002)	Similar (~35%)	71% vs 64% (p=0.18).	PFTs provide prognostic information in HF.
Plesner[47]	39%;	573	2009-2011	Denmark	Chronic at first visit/LVEF<45%	Similar: 75% vs 78%	88% vs 94% (p=0.03)	LD: 64% vs 48% (p<0.01)	Abnormal spirometry predicted ACM.
Yoshihisa[48]	28%	378	2009-2012	Japan	Acute, ~50% HFpEF/Framingham criteria	67% vs 79% (p=0.014)	Similar (87%)	NR	PFTs provide prognostic information in HF.

Table 3: prevalence of COPD in patients with HF, in selected recent registries and clinical trials. Abbreviations used: ACM - all-cause mortality; LD – loop diuretic, BB – beta-blockers; LVEF – left ventricular ejection fraction; HFpEF – heart failure with preserved LVEF; HFrEF – heart failure with reduced LVEF; CV – cardiovascular; HFH – heart failure hospitalisations. PFTs – pulmonary function tests; IV – intravenous.