

Review

# Heart failure and chronic obstructive pulmonary disease: An ignored combination?

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## Abstract

**Aims:** To quantify the prevalence of heart failure and left ventricular systolic dysfunction (LVSD) in chronic obstructive pulmonary disease (COPD) patients and vice versa. Further, to discuss diagnostic and therapeutic implications of the co-existence of both syndromes.

**Methods and results:** We performed a Medline search from 1966 to March 2005. The reported prevalence of LVSD among COPD patients varied considerably, with the highest prevalence (10–46%) among those with an exacerbation. One single study assessed the prevalence of heart failure in COPD patients. A prevalence of 21% of previously unknown heart failure was reported in patients with a history of COPD or asthma. We did not find any report on COPD in heart failure or LVSD patients.

Diagnosing heart failure in COPD patients or vice versa is complicated by overlap in signs and symptoms, and diminished diagnostic value of additional investigations.

In general, pulmonary and heart failure ‘drug cocktails’ can be administered safely to patients with concomitant COPD and heart failure, although (short acting)  $\beta$ 2-adrenoreceptor agonists and digitalis have potentially deleterious effects on cardiac and pulmonary function, respectively.

**Conclusion:** Although knowledge about the prevalence of concomitant heart failure in COPD patients and vice versa is scarce, it seems that the combined presence is rather common. In view of diagnostic and therapeutic implications, more attention should be paid to the concomitant presence of both syndromes in clinical practice and research.

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**Keywords:** Heart failure; Chronic obstructive pulmonary disease; Prevalence; Review

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## 1. Introduction

Clinicians in both primary and secondary care are often confronted with elderly dyspnoeic patients [1]. Major causes for dyspnoea in the elderly are heart failure and chronic obstructive pulmonary disease (COPD) [2]. Both syndromes have been studied extensively, but largely separately, with COPD in the domain of the pulmonologist and heart failure in the domain of the cardiologist. Studies on the prevalence of heart failure in COPD patients or vice versa are scarce. Since presence of one syndrome in the presence of the other has important therapeutic implications, knowledge about the concomitant prevalence is clinically relevant.

Several studies provided some evidence that the syndromes often co-exist. Diagnostic studies showed that pulmonary dysfunction and use of pulmonary medication for example, often coincide with unrecognised heart failure [3], and that unrecognised heart failure is common in COPD patients experiencing acute dyspnoea [4]. Moreover, tobacco smoking is an important common aetiological factor in COPD and heart failure.

We hypothesised that the combination of heart failure and COPD is much more common than generally acknowledged. We reviewed the existing literature to estimate the prevalence of heart failure or left ventricular systolic dysfunction (LVSD) in COPD patients and vice versa. In addition, we discuss diagnostic and therapeutic implications of the co-existence of both syndromes.

## 2. Methods

A Medline search was conducted from 1966 to March 2005. We used the MESH terms ‘pulmonary disease, obstructive or COPD’, ‘heart failure, congestive’, ‘cor pulmonale’ and ‘dyspn(o)ea’. Additional references were retrieved by citation tracking of relevant publications. Only studies published in English were included in the analysis. To quantify the prevalence of heart failure or LVSD in COPD patients, we only included studies that reported left ventricular ejection fractions (LVEF) assessed by either echocardiography, radionuclide or angiographic ventriculography.

Ideally, the prevalence of heart failure or LVSD in COPD patients should be assessed in a representative sample of patients with *objective* evidence of COPD, with diagnostic measurements in *all* eligible patients, using state-of-the-art methodology [5]. In case of COPD, an adequately

performed spirometric pulmonary function test with application of the GOLD criteria is presently considered the reference (‘gold’) standard [6]. Echocardiography is the cornerstone in the diagnostic assessment of heart failure because of its ability to provide information about systolic and diastolic ventricular function, but echocardiography alone is not considered the reference (‘gold’) standard [7]. An acceptable proxy reference is the consensus of an outcome panel that determines the presence or absence of heart failure by using all available diagnostic test results, including echocardiography [8].

## 3. Definitions

For COPD, we used the definition of the Global Initiative for COPD (‘GOLD’) [6], i.e. a disease state characterised by airflow limitation that is not fully reversible. A ratio of post-dilatory forced expiratory volume in one second divided by forced vital capacity (FEV1/FVC) < 70%, assessed by spirometry confirms the presence of COPD, either with or without symptoms compatible with chronic pulmonary disease (cough, dyspnoea, sputum production). Heart failure was defined according to the European Society of Cardiology (ESC) [7], i.e. clinical symptoms and objective evidence of cardiac dysfunction (systolic and/or diastolic). Left ventricular systolic dysfunction (LVSD) was defined as a LVEF < 50% assessed by echocardiography, radionuclide or angiographic ventriculography.

‘Isolated’ right sided heart failure was defined as the presence of signs of right sided heart failure (i.e. elevated central venous pressure, peripheral oedema and/or liver enlargement), increased right atrial pressure and a LVEF > 50%.

## 4. The magnitude of the problem

### 4.1. Prevalence of heart failure or LVSD in COPD patients

We divided studies into those that excluded patients with known coronary artery disease and studies that did not, because the prevalence of heart failure is clearly influenced by presence or absence of coronary artery disease.

All 12 studies that excluded patients with known coronary artery disease included small numbers of participants, with mean ages ranging from 53 to 68 years. Nine of these 12 studies were performed in stable, mostly severe COPD patients. In four (comprising 98 COPD patients in

total) of these nine studies, the prevalence of LVSD (LVEF<40–50%) was zero [9–12] and in five studies (comprising 283 COPD patients in total) the prevalence of LVSD ranged from 3.8% to 16% [13–17].

Three studies were performed in patients experiencing an exacerbation (worsening) of their COPD. One study, with only 10 COPD patients (all with pulmonary artery hypertension), reported zero patients with LVSD [18]. The other two studies (comprising 99 patients in total) reported a prevalence of 23% and 32% LVSD, respectively [19,20].

Six studies included ‘unselected’ COPD patients, that is, without exclusion of patients with known coronary artery disease. The mean age in these studies ranged from 59 to 74 years (Table 1). Five studies in more or less stable COPD patients showed prevalence rates of LVSD ranging from 10% ( $n=27$ ) to 46% ( $n=37$ ) [21–25]. One study, a sub-study of the Breathing Not Properly (BNP) trial, was performed in patients with a known history of asthma or COPD, who had acute dyspnoea urging them to visit an emergency department [4]. Prevalence of LVSD (LVEF<45%) in this study was 18%. The prevalence of previously unknown heart failure was 20.9% [4]. Importantly, however, in only 29% of all participants echocardiography was performed and the diagnosis of heart failure was based on the opinion of two cardiologists [4]. The cardiologists based their diagnosis on the heart failure scores of Framingham [26] and National Health and Nutrition Examination Survey (NHANES) [27], scores that only include elements from history, physical examination and chest radiography. In an unspecified sample of the participants, additional information was available from electrocardiography or further cardiac testing [4].

#### 4.2. Prevalence of COPD in LVSD or heart failure patients

We could not find any report on prevalence of COPD in patients with LVSD or (a history of) heart failure.

Three studies assessed pulmonary function in patients with heart failure and left ventricular dysfunction, but no data were provided on the prevalence of COPD in these patients [28–30]. In five studies among patients with acute dyspnoea, the concomitant presence of COPD and heart failure was assessed [2,31–34]. These studies, however, included patients without a diagnosis of heart failure or COPD at the start of the investigations. Consequently, these studies were not included in our review.

### 5. Diagnostic difficulties

Recognising heart failure in the presence of COPD and vice versa is complicated by similarities in symptoms and physical findings [35,36]. Furthermore, chest radiography is less sensitive for detecting heart failure because the cardiothoracic ratio is adversely affected by hyperinflated lungs and left ventricular dilatation can be masked by right ventricular enlargement caused by COPD [37]. Moreover, in severe COPD, some degree of pulmonary congestion and even pulmonary oedema can be present on chest X-ray, without manifest heart failure [36]. Electrocardiographic abnormalities reported in COPD patients overlap with those seen in heart failure [38]. Natriuretic peptides such as B-type natriuretic peptide (BNP) and amino-terminal pro B-type natriuretic peptide (NT-proBNP) can help the clinician in differentiating COPD from heart failure in patients with acute dyspnoea [2,32,34]. Natriuretic peptide levels can be

Table 1

Studies that assessed heart failure or left ventricular systolic dysfunction in COPD patients, *without* exclusion of patients with known coronary artery disease

First author	Steele [23]	Kline [21]	Berger [24]	MacNee [25]	Zema [22]	McCullough [4]
Year of publication	1975	1977	1978	1983	1984	2003
Sample size	120	27	36	45	37	417
Patient population	Severe COPD	COPD, suspected LV dysfunction	Stable ambulatory COPD	Hypoxemic COPD	Suspected for COPD	History of COPD or asthma, with acute dyspnoea <sup>a</sup>
Mean age	60	62	67	59	61	62
Reference test	RVG	RVG, echo	RVG	RVG	RVG	2 cardiologists <sup>b</sup>
All patients reference test?	No. Only in 30%	No. Only 74% with echo studied	Yes	Yes	Yes	No. Echo in 29%
Exclusion of overt coronary artery disease?	No. 17% had CAD	No, but none of the patients had a history of prior MI	No. 9% known with CAD	No	Partly <sup>c</sup>	No. 30% had CAD
LVSD	21% LVEF<40%	10% LVEF<40%	14% LVEF<40%	36% LVEF<50%	46% LVEF<50%	18% LVEF<45%
Heart failure	NA	NA	NA	NA	NA	21%
Remarks						33% cor pulmonale <sup>d</sup>

CAD, coronary artery disease; ED, emergency department; NA, not assessed; NS, not stated; MI, myocardial infarction; RVG, radionuclide ventriculography.

<sup>a</sup> Patients not known to have heart failure, experiencing acute dyspnoea urging them to visit the emergency department.

<sup>b</sup> Two cardiologists independently based the diagnosis of heart failure on the Framingham and NHANES scores. Additionally, echocardiogram (in 28.5% of the patients) and other clinical tests were used when available for the diagnostic assessment of heart failure.

<sup>c</sup> Exclusion of coarctatio aortae, valve disease, atrial septal defect and  $\beta$ -blocker use.

<sup>d</sup> Cor pulmonale was assessed clinically, that is, a history of obstructive or restrictive lung disease plus hepatic congestion or peripheral oedema on physical examination.

increased in acute hypoxemic COPD, although not as high as in manifest heart failure, possibly due to pressure and/or volume load on the right ventricle [39]. Pulmonary function tests in patients with heart failure show intermediate reduction of pulmonary function at a level between healthy subjects and COPD patients [31]. Echocardiographic windows are limited by hyperinflated lungs and can complicate precise measurements in up to 10–30% of COPD patients [3,12]. Cardiovascular magnetic resonance imaging (CMR) could serve as an alternative for echocardiography in these patients since CMR is not affected by hyperinflated lungs. Moreover, visualisation and measurements of the right ventricle are easier with CMR and right ventricular function can be measured [40]. Disadvantages are the time-consuming data-acquisition and post-processing and the higher cost of CMR compared to echocardiography [40].

## 6. Therapeutic implications

### 6.1. Pulmonary medication influencing cardiac function

The most important treatment options for COPD are  $\beta_2$ -adrenoreceptor agonists and anticholinergics.  $\beta_2$ -Adrenoreceptor agonists are not highly selective and thus  $\beta_1$  receptors predominantly present in myocardial tissue might also be activated. Increased stimulation of these myocardial  $\beta_1$  receptors may eventually accelerate the down regulation of these receptors with increased myocardial oxygen consumption and endogenous catecholamine production as a result [41]. A limited number of studies showed that oral and inhaled short-acting  $\beta_2$ -adrenoreceptor agonists do seem to increase the risk of mortality and number of heart failure exacerbations in patients with left ventricular dysfunction [41,42].

Currently, inhalation of long-acting  $\beta_2$ -adrenoreceptor agonists is preferred in most COPD patients. These drugs are more quickly removed from myocardial and kidney  $\beta$  receptors, thus making potentially deleterious cardiac effects less likely [43].

Anticholinergics can reduce acetylcholine release over a short period [44], and thus these drugs could potentially exert (adverse) cardiac effects conform atropine. Until now, no adverse effect on cardiac function has been described, but the numbers of reliable studies are small [44].

### 6.2. Cardiovascular medication influencing pulmonary function

Treatment options for heart failure include diuretics,  $\beta$ -blocking agents, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARB), aldosterone antagonists and digitalis.

High dosages of diuretics can cause acid–base disturbances (metabolic alkalosis) in COPD patients and this may

blunt the respiratory drive, but at normal dosages pulmonary function is not influenced by diuretics [45].

Until recently, authors advised against the use of  $\beta$ -blocking agents in COPD, notably in the presence of bronchospasm [46]. The reported detrimental effects of  $\beta$ -blocking agents in COPD patients, however, pertained to short-term effects on pulmonary function of (non-selective)  $\beta$ -blockers [46]. A recent systematic review showed that cardioselective  $\beta$ -blocking agents can be administered safely to COPD patients, even in those patients with some bronchospasm, with no or only small negative long-term effects on pulmonary function [47].

The renin–angiotensin system exerts its activity not only in the systemic circulation, but also in organ tissues, such as the lungs [48]. Angiotensin-II is a potent pulmonary airway constrictor. Therefore, ACE inhibitors and ARBs confer potential benefit in treating patients with COPD by decreasing angiotensin-II levels and thus pulmonary obstruction. ACE inhibitors may have additional beneficial effects because they can also decrease pulmonary inflammation and pulmonary vascular constriction [48], and ameliorate the alveolar membrane gas exchange [49].

Aldosterone antagonists such as spironolactone may also have positive effects on gas diffusion, because aldosterone can damage the alveolar-capillary membrane [50].

Digitalis may, however, reduce lung function because it can cause pulmonary vasoconstriction [45].

## 7. Discussion

Our review of the literature shows that precise data about the prevalence of left ventricular systolic dysfunction (LVSD) or heart failure in patients with chronic obstructive pulmonary disease (COPD) or vice versa are still lacking. The available data, however, suggest that in ‘unselected’ COPD patients (range 10–46%) and in COPD patients experiencing an exacerbation (23–32%) the prevalence of LVSD is common. LVSD is not very common (0–16%) in ‘selected’ COPD patients, that is, with exclusion of those with a history of coronary artery disease. The only study assessing (previously unknown) heart failure in patients with a history of COPD or asthma showed prevalence rates of 21%. To our knowledge, no study assessed the prevalence of COPD in patients with LVSD or heart failure.

Diagnostic assessment of one disease in the presence of the other is complicated by the overlap in signs and symptoms [35,36], and a decreased sensitivity of additional tests such as chest X-ray, ECG, but also echocardiography and pulmonary function testing. Multiple testing is necessary to establish whether a particular patient has heart failure, COPD, both or neither. Natriuretic peptides [32,34] and cardiovascular magnetic resonance imaging [40] may be helpful in the diagnostic work-up. The best diagnostic strategy, however, to assess patients with suspected co-existence of both diseases remains to be determined. For this

purpose, diagnostic studies performed in an adequate patient domain are needed [5,8] collecting all relevant diagnostic test results from history, signs and symptoms, ECG, chest X-ray, pulmonary function tests, natriuretic peptides, echocardiography and CMR. The results of (combinations of) these tests should than be compared to the presence of either or both diseases, ideally assessed by a multidisciplinary panel since a 'gold' reference standard for heart failure is lacking.

In general, pulmonary and heart failure 'drug-cocktails' can be administered safely to patients with concomitant COPD and heart failure, although (short acting)  $\beta_2$ -adrenoreceptor agonists and digitalis have potentially deleterious effects on cardiac or pulmonary function, respectively. Cardioselective  $\beta$ -blocking agents can be administered safely to COPD patients since no relevant long-term effects on pulmonary function have been established.

Currently, many of the possible interactions between both syndromes are still unclear, and more extensive knowledge is important in view of the potential increasing prevalence of both diseases in the near future, the possibly common existence and the potential benefit of adequate treatment. More studies should be directed at assessing the prevalence of heart failure in patients with COPD. *Visa versa*, the prevalence of COPD in heart failure patients should be quantified. In addition, the role of the alveolar-capillary membrane in both diseases should be studied further, because this membrane, which is situated directly between the lungs and the heart, seems crucial in the transportation of oxygen.

To achieve this, closer cooperation between general practitioners, cardiologists and pulmonologists is necessary, both in practice and in research.

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