

Heart failure, chronic obstructive pulmonary disease, and asthma: numbers, facts, and challenges

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Abstract

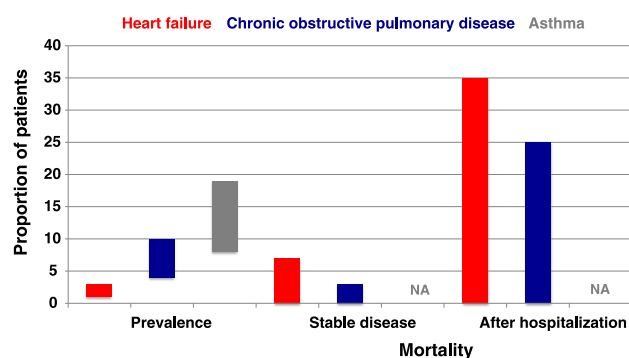
Heart failure (HF), chronic obstructive pulmonary disease (COPD), and asthma are considered as major health problems. They affect 1–3%, 4–10%, and 8–19% of population, respectively, and frequently coexist. Pulmonary function testing and echocardiography are needed for reliable diagnosis, but in clinical practice, diagnosis often is based on history and disease self-reporting. Concomitant HF can be diagnosed in about 20% of patients with COPD, and at least 50% had systolic dysfunction. In patients with HF, prevalence of COPD is up to 35%, and less than 25% of patients have COPD GOLD stage III or IV. COPD is more severe in patients with HF with preserved ejection fraction. When HF and COPD coexist, hazard of death is increased for 39% but can even exceed the mortality in individual disease by threefold. In patients with acute deterioration, natriuretic peptides and lung ultrasound, along with other laboratory biomarkers and imaging, need to be implemented to differentiate underlying cause and to manage patients accordingly. COPD is not contraindication for beta-blockers, and if used, the risk of death is reduced by 31%; if indicated, cardio-selective agents can be used in asthma. Recent pan-European registry reported that about 90% of patients with HF receive beta-blockers, whereas dosing remains a large unmet need with only 17% being treated with target daily dose. Concurrent HF and COPD reduce the prescription of beta blockers threefold, which results in about 20% of patients actually being treated with beta-blockers. In COPD/asthma, beta-agonists are strongly associated with new HF (relative risk of 3.41) and HF hospitalizations (odds ratio of 1.74).

Introduction

Non-communicable chronic disease represents a major burden worldwide, irrespective of individual country wealth and economic situation.¹ Obstructive pulmonary disease (chronic obstructive pulmonary disease—COPD and asthma) and heart failure (HF) remain important challenge for modern medicine, both from diagnostic as well as management perspective. Latter is in particular relevant as all three entities significantly impair patient quality of life and, primarily HF and COPD, also shorten life expectancy. Although attracting significant interest of scientific community and industry, no relevant therapy to improve outcome in COPD and HF with preserved ejection fraction is available to date.^{2–4} In fact, about half of patients in the community remain undiagnosed, and for those with diagnosis, more than half is left with symptomatic relief only.⁵ As diseases share risk factors, they frequently walk hand-in-hand; because of similarities in

clinical presentation, accurate diagnosis, particularly during acute decompensation is challenging and initial treatment may be targeting wrong organs.⁶ Even when stable, HF may alter pulmonary function findings or COPD may limit cardiac imaging to a degree when reliable diagnosis is doubtful. Similar apply to natriuretic peptides as we need to acknowledge concentrations can be elevated because of right ventricular overload only.⁷ In clinical practice, wrong diagnosis or inappropriate interpretation of drug–disease interaction can reduce treatment with life-saving medications. Probably the most prominent case can be argued for beta blockers; guidelines provide robust evidence supporting use of bisoprolol, carvedilol, metoprolol succinate, and nebivolol in HF, with clear statement that COPD is not a contraindication.² GINA guidelines take this one step further, suggesting that most of asthma patients can be safely treated with cardio-selective beta blockers.⁴ On the other side, COPD specific therapy appears to induce cardiovascular events.⁸ Management in

Figure 1 Prevalence and outcome in heart failure, chronic obstructive pulmonary disease, and asthma.



clinical practice, however, has witnessed a development over last decades. Even if latest registry data report on overwhelming success, this needs to be interpreted with significant caution as registries report on hospitalized or ambulatory patients without any good reflection of primary care management.⁹ With these caveats in view, rest of the paper will present the current knowledge, highlight challenges and try to anticipate the future in the field.

Numbers

Prevalence and outcome differ significantly between COPD, asthma, and HF (Figure 1). Although HF has lowest prevalence of up to 3%, survival is worse than in most common malignancies¹⁰ with median survival time after hospitalization of about 2 years. COPD prevalence is estimated between 4 and 10%,

and if stable, annual mortality is about 3%. This increases sharply after hospitalization when about ¼ of patients will die within one year.^{7,11} Certain degree of variety between studies needs to be emphasized, but data are more or less consistent in adults of similar socioeconomic background. For asthma, prevalence is higher (up to 19%) and larger variety exists, likely because of common onset in childhood.¹² Generally speaking, well managed asthma should not reduce life expectancy, but disease burden in terms of years lived with the disease is only modestly less than for COPD and HF.¹³

For this paper, epidemiology of concomitant diseases as well as prognostic implications is relevant. Even today, well-conducted large-scale epidemiological studies about prevalence of concomitant obstructive pulmonary disease and HF are scarce (Table 1). Moreover, data about concurrent HF and asthma are largely absent. For COPD and HF, it may be estimated that about 20–35% will have both diseases, which depends on patient characteristics (age, setting), diagnostic criteria and type of measurement (i.e. good clinical practice for pulmonary function testing and echocardiography), and study design.^{14–18} Prevalence of COPD in HF seems to be equally distributed between patients with reduced and preserved ejection fraction and less than 25% of patients have severe or very severe COPD.^{14–16} Patients with preserved left ventricular ejection fraction have more severe COPD as determined through Tiffeneau index (0.69 vs 0.74, $p < 0.01$).¹⁵ When HF was diagnosed in COPD, 50%–80% of patients have had reduced left ventricular ejection fraction.^{17,18} In a large series from primary care, average left ventricular ejection fraction in concomitant COPD and HF was 45%.¹⁸ Because COPD is more prevalent, it is very likely that in general population COPD is masking a significant cohort of patients with HF.^{17,18} Whatever the main disease, concurrent COPD and

Table 1 Selected studies investigating comorbid chronic obstructive pulmonary disease and heart failure

Main disease and study	Patients	Comorbidity	Main findings
Heart failure			
Portugal ¹⁴	186 (67 y, 70% men)	COPD 39%	COPD diagnosed with pulmonary function testing in stable out-patients; 23% had severe or very severe COPD; no difference in beta blocker use between COPD and no-COPD (86% vs 88%)
ECHOS-Lung Study group ¹⁵	527 (72 y, 63% men)	COPD 35%	COPD diagnosed with pulmonary function testing in patients admitted with HF: 43% of patients with COPD has self-reported COPD and 33% of patients with self-reported COPD had no COPD; patients with preserved left ventricular ejection fraction have more severe obstruction (Tiffeneau index 0.69 vs 0.74, $p < 0.01$); no difference in beta blocker use between COPD vs no-COPD (27% vs 29%)
Italy ¹⁶	118 (73 y, 86% men)	COPD 30%	COPD diagnosed with pulmonary function Testing in outpatients; 23/36 (64%) patients were unaware of any pulmonary disease; 6% had severe COPD; no difference in beta-blocker use between COPD and no-COPD
Chronic obstructive pulmonary disease			
Italy ¹⁷	218	HF 17%	COPD out-patients with echocardiography; 30/37 patients had left ventricular ejection fraction $\leq 40\%$
Netherlands ¹⁸	(70 y, 76% men) 405 (73 y, 55% men)	HF 20%	Primary care patients underwent pulmonary function testing and echocardiography; 42/83 patients had systolic HF (32 had left ventricular ejection fraction $\leq 40\%$), average left ventricular ejection fraction was 45%

HF increase the risk of death that remains evident even after adjustment for beta-blocker therapy⁷; the increase depends upon study population, length of follow-up, and endpoint(s) collected. In a recent meta-analysis¹⁹ that included five studies with 7121 patients, adjusted hazard ratio for all-cause mortality risk was 1.39 (95% confidence interval 1.21–1.60) but the risk can even exceed hazard ratio of 3 in specific study populations.⁷

Facts

Even though epidemiological studies are heterogeneous in study design, population, and main findings, prognostic implications of concurrent HF and COPD remain. For daily practice and management it is therefore vital to establish whether patients have concurrent disease. Here, clinician is faced with several issues that need to be taken into account. Airway obstruction as defined by GOLD is diagnosed when FEV1/FVC ratio is <0.70. This requires pulmonary function testing, and bronchodilator test is warranted to discriminate between reversible (asthma) and irreversible (COPD) airway obstruction.^{3,4} In clinical practice, unfortunately, mostly baseline measurements (i.e. no bronchodilator test) are performed. HF can affect pulmonary function tests in a distinctive manner: restrictive pattern is hallmark of stable disease whereas lung volume overload as seen in acute deterioration can cause obstructive pattern. For definite diagnosis of COPD in HF, initial screening should also include a relevant smoking history (COPD very unlikely in never-smokers), and should pursue repetitive tests if inconclusive or in conflict with other clinical information. COPD has several effects on respiratory and cardiovascular systems that may limit optimal cardiac imaging, particularly during the transthoracic echocardiography. Poor visibility because of lung hyperinflation, ventricular interdependence, atrial fibrillation are some of the challenges for echocardiography interpretation.^{6,7}

In patients with definitive diagnosis of COPD and HF, several therapeutic challenges exist. Over the recent years, fear of beta-blockers seems to fade away; whilst this is true for treatment initiation, many patients remain undertreated. In the last report from pan-European registry with 12 440 patients, beta blockers were prescribed to 72% of hospitalized and 89% of ambulatory patients. However, only 17% of patients were treated with target daily doses.⁹ According to same registry, only 3% of patients have true contraindication for beta-blockers, which is in line with several smaller studies that investigated feasibility and safety of beta-blockers in concurrent HF and COPD.^{20,21} In concurrent COPD and HF, odds to receive beta blockers are about one third and in general, less than 20% of these patients receive beta blockers. In a large sample from primary care (N = 377 439), prevalence of COPD in HF was 25% but only 18% of these were treated with beta blockers (odds ratio 0.30, 95% confidence interval 0.28–0.32).²² Similar information comes from a study in

hospitalized patients (N = 638, 17% COPD), as only 12% were treated with beta blockers (odds ratio 0.35, 95% confidence interval 0.19–0.64).²³ If, however, we are able to introduce beta blockers in concurrent HF and COPD, the patients have 31% reduction in mortality (relative risk 0.69, 95% confidence interval 0.62–0.78) as according to large systematic review and meta analysis.²⁴ For patients with COPD, who cannot tolerate (maximal) beta blocker dose, ivabradine appears to be safe and efficient alternative or add-on drug. The SHIFT study included 730 (11%) patients with COPD, in whom Ivabradine was similarly effective and safe as in patients without COPD. Moreover, it could be safely combined with beta-blockers in patients with COPD.²⁵ Along with evidence based medicine standards, we are sometimes faced with therapies that can sometimes potentially induce harm in respective setting. For COPD, the symptomatic benefit is also conferred through anti-cholinergic drugs. The observational studies have demonstrated some safety concern as use of these drugs was associated with increased risk of cardiovascular events, particularly within 3 weeks of drug initiation.⁸ Data from epidemiological studies suggests that use of beta agonists is associated with new cases of HF in COPD/asthma as well as with worse outcome in those with known COPD and HF.⁷ In a large cohort of asthmatics (N = 8098), oral bambuterol increased incidence of new HF over a median follow-up of 288 days with a relative risk of 3.41 (95% confidence interval 1.99–5.86).²⁶ A 74% increase (odds ratio 1.74, 95% confidence interval 1.60–1.98) in HF hospitalizations over a period of 5 years was reported with inhaled beta-agonists in 59 336 patients with COPD or asthma.²⁷

Coming from drugs to non-pharmacological therapy, rehabilitation should be mentioned. For HF and COPD, convincing evidence is available to pursue for implementation in clinical practice.^{2,28} Today, the modalities, timing, and duration are more or less established but we fail to deliver the rehabilitation because of various reasons, mostly logistics and no reimbursement in many countries.

Challenges

Accurate and timely diagnosis of COPD and HF and vice versa remains an unmet need. In stable condition, natriuretic peptides, cardiac imaging, and pulmonary function tests should be performed in patients at risk or with typical symptoms. During acute deterioration, trigger identification is crucial as therapies targeting HF and COPD are to some extent diametrically different and can cause further worsening. The problems with natriuretic peptides were already mentioned thus multimarker strategy was tested. Addition of procalcitonin, D-dimer, and troponin, respectively, to standard laboratory assessment can be helpful for decision taking in emergency room. In the BACH study, a combination of procalcitonin and natriuretic peptides was helpful to qualify patients for antibiotic therapy in cases of pneumonia or pneumonia with heart failure.²⁹

A largely neglected imaging method in acutely deteriorated patients is lung ultrasound. Diagnostic performance for excess lung water, pulmonary infarctions, and even pneumonia is remarkable but rarely implemented in clinical practice.³⁰ With expansion of FOCUS ultrasound, this may change in near future.

Therapy optimization is difficult in multimorbid patients and needs collaboration between many experts. A specialized out-patient setting should be preferred as there is need for serial follow-up to fine tune the management. Standards for HF specialized units are known, and care is delivered accordingly in many European countries.^{31,32} Next step should be more close collaboration between societies when writing position statements and guidelines.

Future

Number of patients with HF and obstructive pulmonary disease is likely to increase around the world.^{1,33} This may

be because of aging, better management of acute conditions, better screening in general and population at risk, and calls for better organization of care.³⁴ With available evidence at hand, we are unlikely to see adequately powered trials with life saving therapy, e.g. beta blockers in patients with concurrent HF and COPD. Irrespective to this, beta blockers appear warranted and safe in comorbid patients.^{20,21} Important information is awaited from the Study to Understand Mortality and Morbidity in COPD (SUMMIT), with endpoints specifically including cardiovascular mortality information.³⁵ Finally, pharmacological management should be optimized to patient needs and minimal effective doses should be used. Through such approach, potential for side effects and clinically relevant drug-drug and drug-disease interactions can be minimized.³⁶

Conflict of Interest

None declared.

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