COPD and pulmonary function in heart failure:

a matter of definition

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CHAPTER 1

Introduction and outline of this thesis

1.1 Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is one of the leading causes of morbidity and mortality in adults all over the world resulting in a substantial socioeconomic burden.[1] According to predictions of the World Health Organization, COPD will become the third leading cause of death, exceeded only by ischemic heart disease and cerebrovascular disease, and the fifth leading cause of disability worldwide by the year 2020.[2] Estimates of COPD prevalence in the general population vary substantially across studies due to geographical variations, differences in survey methods, study population, and collection of spirometric data.[3] Moreover, different diagnostic criteria have been applied, yielding varying COPD prevalence rates.[3] A systematic review and meta-analyses of studies carried out in 28 countries between 1990 and 2004 reported a pooled prevalence of "patient-reported and physician diagnosed COPD" of ~ 5%, reflecting the widespread underrecognition and underdiagnosis of COPD.[3] The pooled prevalence from 26 "spirometric estimates" was ~ 9%, with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) being the most common spirometric definition used.[3] Prevalence rates were higher in elderly (≥ 40 years), smokers, males, and urban residents.[3] The Burden of Obstructive Lung Disease (BOLD) study, including 9425 participants ≥ 40 years old from 12 sites worldwide, has documented higher COPD prevalence rates (11 – 26%) and more advanced staging of "spirometrically confirmed COPD" (GOLD criteria) than previously reported (GOLD stage ≥ II = overall 10%).[4] Using the lower limit of normal (LLN) to define COPD, however, resulted in lower prevalence rates of COPD (~ 8-19%) than the GOLD criteria.[5] Globally, the burden and mortality of COPD is projected to increase in coming decades because of continued exposure to COPD risk factors, ageing of the population, and a decrease of mortality due to other diseases like cardiovascular disease in industrialized countries and infectious disease in developing countries.[6, 7]

COPD is a heterogeneous disease process that varies greatly from person to person with respect to lung pathology, natural history of disease, and co-morbidity.[6] It is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to cumulative exposures over decades to noxious particles or gases.[1] Tobacco smoking is the main risk factor for the development of COPD. However, other factors, such as genetic factors, exposure to indoor and outdoor air pollution, occupational hazards, infections, and chronic asthma are also important.[6, 8] The inflammatory process results in hypersecretion of mucus, structural changes and narrowing of the small airways (chronic obstructive bronchiolitis), and enlargement of air spaces, destruction of lung parenchyma, loss of elasticity, and closure of small airways (emphysema).[1, 9]

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough, and sputum production that can be variable from day-to-day. Additional symptoms may include wheezing, chest tightness, fatigue, weight loss, anorexia, and symptoms of depression/anxiety and cor pulmonale.[1] With increasing severity of disease, patients experience acute exacerbations of COPD, characterized by acute worsening of respiratory symptoms that is beyond normal day-to-day variations and requires change in medication.[1] Exacerbations can be precipitated by several factors, including respiratory tract infections (viral or bacterial), exposure to pollutants, and interruption of maintenance therapy. However, the cause of about one-third of severe COPD exacerbation cannot be identified.[1] Importantly, exacerbations can negatively affect a patient's quality of life, accelerate the rate of lung function decline, and are associated with significant mortality and high socioeconomic costs. One of the treatment goals of COPD is therefore to reduce the frequency and severity of exacerbations.[1]

Spirometry is required for the diagnosis of COPD by measuring persistent airflow limitation. However, there is no consensus on how to define airflow limitation.[10-20] This is further elaborated in **subsection 1.5** of the introduction of this thesis.

It is increasingly recognized that COPD is a complex multi-component disease that extends beyond the lungs. Many patients have systemic manifestations and co-morbidities that can further impair functional capacity and health-related quality of life and can increase the risk of hospitalization, mortality, and costs.[21, 22] Indeed, patients with COPD more frequently die from other causes than COPD,[23] with cardiovascular disease and lung cancer being the commonest causes of death,[24-27] especially in those with mild to moderate COPD.[28] Moreover, co-morbidities may interfere with COPD management.[1] Co-morbidities and extra-pulmonary effects of COPD include cardiovascular disease, skeletal muscle dysfunction, cachexia, pulmonary hypertension, metabolic syndrome, lung cancer, osteoporosis, depression, anemia, and obstructive sleep apnea.[21] Co-morbidities are more commonly seen in association with severe COPD, but they may also be associated with milder disease.[22] Although the mechanism linking COPD to systemic manifestations and co-morbidities is not yet certain, it is though that systemic inflammation is crucial in the pathogenesis.[21, 22, 29, 30] Other possible mechanisms include shared genetic predispositions, cigarette smoking, accelerated ageing, physical inactivity, and chronic hypoxia.[21, 22]

The cornerstone of COPD treatment is smoking cessation which has the greatest capacity to influence the natural history of COPD.[31] Other non-pharmacological therapeutic options are rehabilitation, nutritional advice, oxygen therapy, ventilatory support, lung volume reduction therapies such as bullectomy and valve placement,

lung transplantation, and palliative care. Pharmacological treatment of COPD includes bronchodilators, corticosteroids, phosfodiesterase-4 inhibitors, vaccines, alpha-1 antitrypsin augmentation therapy, antibiotics, mucolytic and antioxidant agents, antitussives, and narcotics (morphine).[1]

1.2 Heart failure

Heart failure (HF) is defined according to the European Society of Cardiology (ESC) guidelines[32] as a clinical syndrome in which patients have typical symptoms and signs resulting from an abnormality of cardiac structure or function. HF often results in diminished quality of life, declining functional capacity, episodes of decompensation leading to hospital admission, and premature death, usually due to pump failure or a ventricular arrhythmia.[32, 33] Typical symptoms of HF include breathlessness, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, ankle swelling, and fatigue. Less typical symptoms are nocturnal cough, wheezing, weight gain or loss, bloated feeling, loss of appetite, confusion, depression, palpitations, and syncope.[32] There is a poor relationship between symptoms and the severity of cardiac dysfunction. Symptoms do relate more closely to prognosis if persistent after therapy and can be used to classify the severity of HF (New York Heart Association (NYHA) class) and to monitor the effects of therapy.[32] Signs of HF may include elevated jugular venous pressure, hepatojugular reflux, third heart sound, laterally displaced apex beat, cardiac murmur, peripheral edema, pulmonary crackles, reduced air entry and dullness to percussion at lung bases, tachycardia, irregular pulse, tachypnea, hepatomegaly, ascites, and cachexia.[32] Many of the symptoms and signs of HF are not specific and, therefore, of limited diagnostic value. Demonstration of an underlying cardiac cause for these symptoms and signs by obtaining objective evidence of a structural or functional cardiac abnormality is therefore central to the diagnosis of HF.[32] This is usually myocardial disease causing systolic ventricular dysfunction. However, abnormalities of ventricular diastolic function or of the valves, pericardium, endocardium, heart rhythm, and conduction can also cause HF and more than one abnormality can be present.[32]

Approximately 1–2% of the adult population in developed countries has HF, with the prevalence rising to ≥ 10% among persons 70 years of age or older, while persons younger than 50 years are hardly ever found to have HF.[32, 33] The life time risk of developing HF is approximately 20% for all individuals older than 40 years.[34] The number of patients with HF is predicted to increase due to the ageing of the population, improvements in the treatment of acute coronary syndromes, and a longer survival of patients with HF.[33]

Two types of HF related to the measured ejection fraction (EF) have been recognized, i.e. HF with a reduced EF (HF-REF), or 'systolic HF', and HF with a preserved EF (HF-PEF), or 'diastolic HF'.[32] Approximately half of patients with HF have preserved EF.[35, 36] Whether HF-PEF and HF-REF are two distinct entities or two ends of a common spectrum remains a matter of debate.[36, 37] Amongst many causes of HF-REF, coronary artery disease is the cause of approximately two-thirds of cases of HF-REF.[32] Patients with HF-PEF, on the contrary, are less likely to have coronary heart disease and more likely to have hypertension and atrial fibrillation (AF).[35, 38, 39] Moreover, patients with HF-PEF are older, more often female and obese, and seem to have a better prognosis than those with HF-REF,[33, 35, 39] although not all studies could confirm this latter finding.[38, 40, 41] Also, the diagnosis of HF-PEF is more challenging than the diagnosis of HF-REF, because it is largely one of exclusion; potential non-cardiac causes of the patient's symptoms, such as anemia or chronic lung disease, must first be discounted.[32] Moreover, there is no universally agreed upon definition to diagnose HF-PEF.[41] The left ventricular EF (LVEF) is normal or only mildly reduced in HF-PEF.[32] A cutoff point of 50% LVEF was used in the consensus statement on the diagnosis of HF with normal LVEF by the HF and echocardiography associations of the ESC.[42] Patients with a LVEF in the range 35–50% represent a 'grey area' and most probably have primarily mild systolic dysfunction.[32] Usually, patients with HF-PEF do not have a dilated heart and many have an increase in LV wall thickness and increased left atrial size. Most have evidence of diastolic dysfunction, which is generally accepted as the likely cause of HF in these patients.[32] Diastolic LV dysfunction, however, is not unique to patients with HF-PEF, but also occurs in patients with HF-REF, in whom it even correlates better to symptoms than LVEF.[42]

It is important to identify the underlying cardiac problem, as the precise pathology determines the specific treatment used.[32] The goals of treatment are to relieve symptoms and signs, prevent hospital admission, and improve survival.[32] Although several pharmacological treatment options exist for patients with chronic HF-REF, such as diuretics, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) in case of intolerance, beta-blockers, and mineralocorticoid/aldosterone receptor antagonists, no effective treatment has been identified in patients with HF-PEF in order to reduce morbidity and mortality.[32, 36, 43] Diuretics are used to relieve symptoms and signs in patients with HF-PEF. Also, adequate treatment of hypertension, myocardial ischemia, and AF is considered to be important for which calcium-channel blockers may be used, contrary to patients with HF-REF, in whom their negative inotropic action can be dangerous.[32] Other treatment modalities for HF are described elsewhere in detail,[32] including treatment of acute HF/cardiogenic shock, exercise training, implantable cardioverter-defibrillator, cardiac resynchronization therapy, treatment of arrhythmia or severe bradycardia/conduction

disturbances, coronary revascularization, surgery (valve surgery, ventricular assist devices, transplantation), and palliative care. Finally, management of co-morbidities such as COPD is important, as they may influence treatment and prognosis of HF.[44, 45]

1.3 COPD in HF and vice versa

COPD and HF are both common diseases with significant morbidity, mortality, and health care use.[44, 45] Moreover, COPD and HF seem to coexist more frequently than expected from their separate population prevalences.[46] Several factors might explain the high coexistence of these two diseases, including sharing of environmental (mainly smoking) or genetic risk factors, advanced age, systemic inflammation,[45, 47-53] and a relationship between a reduction in pulmonary and heart function.[54-58] Also, COPD patients are at an increased risk of co-morbidities, such as metabolic syndrome, which in turn are an important risk for cardiovascular disease.[59] Furthermore, factors that increase stress on the cardiovascular system or precipitate arrhythmic events can also explain the association between COPD and cardiovascular disease, including hypoxemia, hyperinflation, hyperventilation, neurohumoral disturbances, increased work of breathing and oxygen consumption, pulmonary hypertension, and the use of pulmonary medication.[48, 53, 60-65] Finally, other factors, such as oxidative stress, endothelial dysfunction, arterial stiffness, hypercoagulable state, and connective tissue degradation have also been suggested to play a role.[48, 60, 62, 66]

The combination of both diseases presents many diagnostic and therapeutic challenges as well as adverse prognostic implications.[44-47, 67-75] Several difficulties in diagnosing COPD in patients with HF and vice versa have been put forward, all of which may lead to misdiagnosis or delay in the diagnosis. These include the overlap in symptoms, signs, and risk factors, misinterpretation of radiological evidence of HF due to chest hyperinflation and pulmonary vascular remodeling, poor acoustic windows of transthoracic echocardiography due to air trapping, lower diagnostic accuracy of B-type natriuretic peptide (BNP) in stable patients with COPD and chronic HF (CHF), even more challenging diagnosis of HF-PEF in patients with COPD, the underuse of spirometry, and difficulties with interpreting spirometry results, especially in patients with decompensated HF, who may have both restrictive and obstructive ventilatory defects.[44, 72, 76, 77]

Therapeutic challenges have been stressed as well. COPD may interfere with treatment and clinical course of HF and oppositely. Especially the opposite pharmacological effects of beta-blockers for HF and beta-agonists for COPD have been a reason for concern leading to underuse of beta-blockers.[78-81] Although cardioselective

beta1-blockers are considered to be safe,[82-85] even during hospitalization for COPD,[86] and therefore should not be withheld from patients with COPD and coexisting cardiovascular diseases, the safety profile of non-selective beta-blockers is not as well-established.[82, 85-97] In addition, the cardiovascular safety of beta2-agonists is disputable.[82] Beta2-agonists have been reported to increase the risk of adverse cardiovascular events in patients with obstructive airway disease,[98] with a significant increase in sinus tachycardia and a non-significant trend toward an increase in major cardiovascular events, including ventricular tachycardia, AF, syncope, congestive HF, myocardial infarction, cardiac arrest, and sudden death.[99] On the other hand, a pooled analysis of cardiovascular safety data including 17 randomized clinical trials did not find an increased risk of cardiovascular adverse events as well as deaths comparing salmeterol treatment to placebo in patients with COPD.[100] Similar findings were reported when patients were stratified for age of > 65 years or the presence of known cardiovascular disease.[100] Similarly, cardiovascular mortality and cardiovascular related adverse events were not greater in the salmeterol (+/- fluticasone) group compared to placebo in more than 6000 patients with COPD in the TORCH trial.[25, 101] Observational studies have shown worse outcomes with bronchodilator use in patients with HF, including increased risk of HF hospitalization, increased mortality rates, in-hospital mechanical ventilation, intravenous vasodilator use, and major cardiovascular events associated with the use of beta-agonists,[82, 102-104] although not all could confirm these findings.[105] Possible mechanisms for adverse cardiovascular outcomes are arrythmogenesis, ischemia, hypoxemia, inflammation, cardiac remodeling, QTc prolongation, metabolic alterations (hypokalemia), and/or attenuation of beta-blocker benefits.[82, 98, 103] In addition, hepatic metabolism of beta2-agonists may be diminished in patients with HF, leading to prolonged plasma half-life and accumulation with repeated doses.[106]

Inhaled anticholinergics have also been reported to be associated with adverse cardiovascular effects among patients with COPD, including an increased risk of cardiovascular death, myocardial infarction, or stroke,[107-116] although recently reassuring cardiovascular safety data have been reported on the long-acting anticholinergic bronchodilator tiotropium HandiHaler[110, 115, 117-123] as well as Respimat.[124] However, HF patients are usually excluded from clinical trials and the impact of bronchodilators on outcomes has never been prospectively evaluated in patients with HF.[103] Furthermore, methodological limitations of most studies require further investigation of reported adverse events.[82, 103] Until then, bronchodilators, in particular beta-agonists, must be used with caution in patients with underlying cardiac condition such as HF, given the paucity of data in such patients.

Similarly, other medications prescribed for one disease may have detrimental effects on the other. High dosages of diuretics can cause metabolic alkalosis which may blunt the respiratory drive of COPD patients, causing hypoventilation with subsequent worsening of hypercapnia.[75] Moreover, in HF patients with diuretic medication the potassium lowering effect of additive administration of beta2-agonists has to be considered, as it can provoke arrhythmias.[51] Digitalis can cause pulmonary vasoconstriction, reduced venous return and cardiac output, and cardiac arrhythmias due to hypoxia and acidosis in patients with COPD.[75] Also, it has the potential to increase airway obstruction.[68] ACE-I are associated with side-effects such as cough, although according to the review of Packard et. al[125] patients with asthma or COPD were not at an increased risk of developing cough and bronchoconstriction as a result of therapy with ACE-I. Theofylline can predispose to tachyarrhythmias even in the absence of elevated serum drug levels.[126] Finally, oral corticosteroids cause sodium and water retention, potentially leading to worsening of HF, but this is not believed to be a problem with inhaled corticosteroids.[32, 127] Moreover, systemic corticosteroids, unlike inhaled corticosteroids, have been associated with the development of atrial fibrillation and ventricular arrhythmias,[126, 128] possibly due to local potassium efflux, mineralocorticosteroid effect leading to hypertension, development of late potentials, vasodilation, and possible anaphylaxis.[129]

On the other hand, cardiovascular drugs, including statins and ACE-I/ARBs, could have beneficial effects in patients with COPD;[130-135] statins due to their anti-inflammatory, anti-oxidative, and immunomodulatory pleiotropic effects,[131, 132, 136-140] as well as their potential to inhibit smoke-induced airway epithelial injury,[141] and ACE-I/ARBs due to their anti-inflammatory and vasodilator effects as well as their effects on alveolar epithelial cell apoptosis and lung fibroblast growth.[131, 140] However, a recent large multicenter randomized controlled trial (RCT) of 885 moderate to severe COPD patients at high risk for exacerbations and without an indication for statin use did not show beneficial effects of daily treatment with 40 mg simvastatin during 12-36 months versus placebo on exacerbation rate, time to the first exacerbation, or the severity of exacerbations.[142] Simvastatin also had no effect on lung function, general or disease specific quality of life, serious adverse events, or the number of deaths.[142] The underuse of statins in persons with cardiac risk factors who have been included in prior retrospective studies may account in part for the differences in findings. Beta-blockers could theoretically exert beneficial effects in patients with COPD by tempering the sympathetic nervous system or by reducing the ischemic burden.[65, 131] Moreover, chronic use of beta-blockers may decrease airway hyperresponsiveness and inflammation as suggested by animal data and a small pilot study in humans.[131] Recently, long-term treatment with beta-blockers has been shown to reduce the risk of exacerbations and improve survival in patients with COPD, even in the absence of

overt cardiovascular disease, possibly as a result of dual cardiopulmonary protective properties.[143, 144] Furthermore, thrombocytosis is associated with increased short- and long-term mortality after exacerbation of COPD and antiplatelet therapy may have a protective role by lowering 1-year mortality after COPD exacerbation.[145, 146] Similarly, bronchodilation may have positive effects on cardiovascular function by alleviating dynamic hyperinflation,[147] which reduces intrathoracic pressure, thus improving venous return and cardiac output, and lessens the effort of breathing by unloading respiratory muscles.[148] Finally, corticosteroids may play a role in improving cardiovascular outcomes in COPD due to their anti-inflammatory properties,[149-153] although a recent systematic review and meta-analysis of 23 RCTs did not show significant association between the use of inhaled corticosteroids with the reduction in risk of myocardial infarction, cardiovascular death, or mortality.[154] In the observational studies, on the other hand, inhaled corticosteroids were associated with a significant reduction in cardiovascular death and mortality, most probably due to methodological issues.[154]

Patients with concurrent COPD and CHF may benefit from higher levels of positive end-expiratory pressure (PEEP) when managed with supported invasive mechanical ventilation. On the other hand, PEEP levels of 10 cm H2O or greater should be used cautiously in patients with COPD alone, since this can lead to increased dead space ventilation and work of breathing and as a consequence a decrease in minute alveolar ventilation and increased $PaCO_2$ levels.[155]

The prognosis of coexistent COPD and HF is poorer than that in either disease alone. COPD is an independent predictor of death and HF hospitalization in patients with HF,[44, 88, 156-168] although not all studies could confirm this.[169-172] A recent study found COPD to be associated with increased risk of HF hospitalization and major adverse cardiovascular events, but not with 24 months survival in ambulatory HF patients.[173] Similarly, after adjustment for prognostic risk factors, beta-blocker use, and randomized treatment (ivabradine/placebo), coexistent COPD was associated with all-cause hospitalization and hospitalization for worsening HF, but not with all-cause or cardiovascular mortality in ambulatory patients with stable systolic HF in another study.[174] Higher GOLD stage is a predictor of worse prognosis.[175] Long-term prognosis of patients with coexistent HF and COPD is similar in patients with HF-REF compared to those with HF-PEF,[175] although mortality risk has been shown to be higher in patients with HF-PEF in another study.[160] Furthermore, having COPD is associated with decreased functional capacity as measured by the 6-minute walking test[176] and cardiopulmonary exercise testing.[177] Similarly, concurrent HF is an independent predictor of mortality in patients with both stable and exacerbated COPD.[178-182] Furthermore, congestive HF has been found to be associated with a higher risk for

COPD related emergency department visit,[183] hospitalization,[183] and worse self-rated health.[184] Finally, healthcare utilization and costs for concomitant COPD and HF are greater than that in patients with either condition alone.[80, 185, 186]

Despite the close relationship between lung and heart diseases, pulmonologists and cardiologists often focus on their own field of specialization.[70] Meanwhile, HF and COPD often remain an ignored combination[73] and the degree of awareness is low among both cardiologists as well as pulmonologists.[170] In view of diagnostic, therapeutic, and prognostic implications of the coexistence of COPD and HF, more attention should be paid to the concomitant presence of both diseases in clinical practice and research.[73] Moreover, knowledge about the concomitant prevalence facilitates the decision on additional testing in daily practice.[46] Although the occurrence of HF in patients with COPD has been assessed extensively in prior research, the occurrence of COPD in patients with HF has received much less attention.[46]

The prevalence of unrecognized HF has been reported to be 21% in both stable COPD patients from a general practice (54% systolic, 46% isolated diastolic, 0% right-sided HF),[187] as well as patients with a history of COPD or asthma presenting to the emergency department with acute dyspnea.[188] A history of ischemic heart disease, a laterally displaced apex beat, a body mass index > 30 kg/m^2, and a raised heart rate ($>$ 90 beats/min) were independent clinical indicators of the presence of concomitant HF in elderly patients with stable COPD. Raised N-terminal-pro-BNP ($>$ 14.75 pmol/l) and abnormalities on electrocardiography further improved the diagnostic accuracy.[189] The prevalence of LV systolic dysfunction (LVSD, i.e. LVEF $<$ 40-50%) in stable COPD patients without known coronary artery disease (CAD) varied between 0% and 16% (4 out of 9 studies found a prevalence of 0%).[73] When LVSD was found, it was generally mild and mainly in patients with a history of cor pulmonale.[46] In patients without known CAD who were experiencing COPD exacerbation, prevalence varied between 0% and 32%.[73] In groups without exclusion of patients with known CAD, prevalence rates of LVSD ranged from 0% to 46%.[73, 170, 190] In another study, echocardiographic LV dysfunction was found in 51% of patients admitted for a severe acute exacerbation of COPD without an obvious cause, of which 64% was systolic, 23% diastolic, and 13% both. After discharge, an expert panel could confirm in 31% of the acute exacerbations a definite association with LV dysfunction.[191] In a recent study,[192] echocardiography was performed in 342 patients with COPD 3 months after discharge from their first hospital admission for COPD exacerbation. Significant cardiac alterations were present in 64% of the patients; 27% left- and 48% right-heart disorders. The most common were right ventricle enlargement (30%) and pulmonary hypertension (19%; 33% in severe disease and 7% in mild disease). The magnitude of pulmonary hypertension was mild in the majority of

patients and only 3% of patients had systolic pulmonary artery pressures close to out-of-proportion pulmonary hypertension in COPD. Left ventricle enlargement was present in 6%, LV systolic dysfunction in 13% (9% LVEF 40-50%, 4% LVEF 30-40%), LV diastolic impairment in 12%, and left atrial dilatation in 29%. Echocardiographic abnormalities were unrelated to COPD severity and they were also observed in 63% of patients without known cardiac disease or cardiovascular risk factors other than smoking, although left heart abnormalities were more frequent in patients with previous cardiac disease compared to those without known cardiac disease (47% versus 27%).[192] Finally, LV diastolic dysfunction has been found to be highly prevalent (48-88%) in patients with COPD in other studies.[193-198] Interestingly, a recent study found 50% of advanced COPD patients with diastolic dysfunction but without known risk factors for diastolic dysfunction (hypertension, diabetes, ischemic heart disease, and hypothyroidism) to have reversible perfusion defect on stress SPECT myocardial perfusion imaging that were not apparent with stress electrocardiography.[195] This observation suggests that myocardial ischemia is a possible cause of diastolic dysfunction in patients with advanced COPD without risk factors for LV relaxation abnormalities.[195] Several other mechanisms of diastolic dysfunction in COPD have been put forward in the literature, including co-morbidities leading to impaired diastolic relaxation, interventricular dependence with impaired LV filling, hypoxia, prolonged use of beta2-agonists, pericardial restriction due to hyperinflation,[195, 199] accelerated ageing,[200] myocardial fibrosis,[200] and LV hypertrophy which is present in 30% of COPD patients, even when normotensive and normoxemic.[201]

Pulmonary hypertension is a frequent complication of COPD, especially in those with advanced disease and hypoxemia.[202] Estimates of the prevalence of pulmonary hypertension vary widely between 30% and 70% due to differences in definitions of pulmonary hypertension, study population, and methods used to determine pulmonary pressures.[202] The true prevalence of pulmonary hypertension in patients with mild to moderate COPD is unknown because of the absence of large-scale epidemiologic studies.[202] Severe pulmonary hypertension, defined as mean pulmonary artery pressure $>$ 40 mmHg, is uncommon ($<$ 5%) and is typically associated with less severe airflow limitation on the one hand, but more severe hypoxemia and diffusion impairment on the other hand.[202] The pathophysiology of pulmonary hypertension is likely multifactorial: destruction of lung parenchyma with accompanying loss of vascular surface area, hypoxic vasoconstriction and inflammation leading to pulmonary vascular remodeling, and genetic susceptibility.[202] Finally, other co-morbid conditions, such as left-sided heart disease, may contribute.[202] Increase in the pulmonary vascular resistance and pulmonary artery pressure presents an increased afterload to the right ventricle which may eventually lead to ventricular remodeling with hypertrophy and later dilatation of the right

ventricle (cor pulmonale) with subsequent dysfunction.[68, 202, 203] Also, pressure overload of the right ventricle and hypoxemia may lead to right ventricle ischemia, which may further aggravate ventricular dysfunction.[202, 203] Finally, decreased right ventricular preload due to decreased venous return associated with hyperinflation may contribute to right ventricular dysfunction.[54, 57, 202, 204] The same is true for the LV.[57, 200, 204] On the other hand, the increase in the end-diastolic volume (preload) of the right ventricle due to dilatation maintains the cardiac output even as the right ventricle EF decreases.[68] Most patients with COPD-associated pulmonary hypertension have preserved right ventricular contractility during stable conditions, while right ventricular systolic failure may be present in the acutely decompensated state.[202] However, subclinical right ventricular dysfunction may be present in patients with mild airflow obstruction[205] and without pulmonary hypertension,[206] while right ventricular hypertrophy has been shown in patients with mild to moderate COPD[196] and in those without pulmonary hypertension[206] and without hypoxemia,[207] suggesting that right ventricular morphological and functional changes could be early signs of pressure overload developing in the initial disease stages.[208] Right ventricular dysfunction may ultimately lead to deterioration of LV function due to interventricular dependence.[68, 202, 203] As the two ventricles are in series, the reduced right ventricular output reduces the LV preload.[55, 68, 202] Moreover, a dilatation of the right ventricle shifts the interventricular septum into the left, changing LV geometry and thereby reducing LV diastolic compliance and end-diastolic volume.[68, 202, 203, 209] On the other hand, the increased right ventricular end-systolic pressure also serves to augment the LV emptying.[68, 210] Due to this complex interplay of opposite forces the LVEF is relatively preserved, even in advanced emphysema.[68]

Estimates of COPD prevalence in patients with HF vary substantially between 9% and 52% in earlier reports that relied on clinical data, disease codes, or self-reported COPD, which is a very inaccurate method for establishing the diagnosis.[44] Indeed, relying on self-report or physician diagnosis of COPD results in approximately one-third to one-half of patients being labeled as having COPD who actually do not fulfill the GOLD criteria for COPD.[77, 187, 211, 212] Although spirometry is considered to be the gold standard for the diagnosis of COPD, data on the prevalence of COPD based on spirometry in patients with HF are scarce and spirometry is widely underused, even in a tertiary care setting.[77] Fortunately, during the past six years more spirometric data on the prevalence of COPD in HF has become available. Nevertheless, prevalence rates of COPD still vary considerably between 9% and 44%, depending on study design, population, and diagnostic criteria used (**Table 1**). Also, a great number of patients is either under- or overdiagnosed with COPD, although exact figures vary across the studies (**Table 1**). Since airway obstruction is a dynamic phenomenon in HF, as it may be present in congestive HF and may disappear with

Table 1 COPD prevalence, under- and overdiagnosis in patients with HF.

Author, yr	Study type	No.	Population	Definition of HF stability	Age, yrs	
Beghé et al., 2013[190]	P	124	Stable CHF, ≥ 50 yrs, ≥ 10 PY	On stable medication for 3m	72 ± 7	
Brenner et al., 2013[157]	P	619	6m after hospitalization for HF, LVEF ≤ 40%	-	65 ± 12	
Miniati et al., 2013[213]	P	260	Hospitalized for systolic HF (LVEF < 50%), evaluation under stable clinical conditions shortly before hospital discharge	-	68 (58-75)^	
Miniati et al., 2013[214]	P	439	Hospitalized for systolic HF (LVEF < 50%), evaluation under stable clinical conditions shortly before hospital discharge	-	68 (? - ?)^	
Boschetto et al., 2013[169]	P	118	Stable systolic/diastolic CHF (< 3m), first outpatient visit, ≥ 65 yrs, ≥ 10 PY	NA	73 ± 7	
Steinacher et al., 2012[215]	P	89	Stable CHF outpatients (HF-REF 97%/HF-PEF 3%)	On stable diuretic therapy, without signs of fluid overload, acute HF, or decompensation as worsening clinical condition	67 (59-76)^	
Arnaudis et al., 2012[159]	R	348	Hospitalized for HF, LVEF ≤ 45%, spirometry < 1w after discharge	-	57 ± 15 (COPD -) 65 ± 11 (COPD +)	
Macchia et al., 2012[170]	P	201	Stable CHF outpatients, LVEF ≤ 40%, ≥ 60 yrs	NA	75 ± 16	
Apostolovic et al., 2011[176]	P	174	Stable CHF outpatients without known COPD, LVEF < 45%, ≥ 65 yrs	No new symptoms, no change in regular therapy, and not seeking medical help < 2w	73 ± 5 (COPD -) 76 ± 6 (COPD +)	

	Men, %	NYHA	LVEF, %	FS/CS, %	Definition of COPD	COPD prevalence, %	Severity of COPD, %	COPD under-/ overdiagnosis, %
	86	I-IV	40 ± 12	100	GOLD (?)	34	GOLD I/II: 52/40 GOLD III: 8	24*
	76	II-IV	42 ± 11	54	GOLD	9	NA	NA / 78
	80	III/IV 32%	32 (25-40)^	CS: 19	LLN + clinical criteria	25	GOLD I/II: 17/63 GOLD III/IV: 20	NA
	79	NA	NA	NA	LLN + clinical criteria	27	NA	NA
	86	I-IV	40 ± 11	100	GOLD LLN	31 29	GOLD I/II: 56/39 GOLD III: 6	64** / NA
	72	I-III	35 (25-40)^	55	GOLD LLN	44 25	GOLD I: 32 (LLN), 77 (LLN -, GOLD+)	68*** / 6***
	76	I-IV	30 ± 10 (COPD -) 33 ± 12 (COPD +)	68	GOLD	38	GOLD I/II: 52/38 GOLD III/IV: 8/3	81† / 4†
	69	NA	32 ± 9	60	GOLD	37	GOLD I/II: 17/48 GOLD III/IV: 33/1	NA
	72	I-III	41 ± 10 (COPD -) 38 ± 9 (COPD +)	44	GOLD	28	NA	28 / NA

Table 1 Continued.

Author, yr	Study type	No.	Population	Definition of HF stability	Age, yrs	
Iversen et al., 2008[211]	P	527	Hospitalized HF patients, HF-REF (59%)/HF-PEF (41%), spirometry 24-72h after admission	-	72 (71-73)[#]	
Mascarenhas et al., 2008[166]	R	186	Stable HF outpatients, LVEF < 45%	NA	67 ± 12	

Data are presented as mean ± standard deviation (SD) and percentages unless stated otherwise. *Underdiagnosis*: proportion of patients without a history of COPD who had airflow obstruction using spirometry during the study. *Overdiagnosis*: proportion of patients with a history of COPD which was not confirmed by spirometry during the study. Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; CS, current smokers; FS; former smokers; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HF, heart failure; HF-PEF, heart failure with preserved ejection function; HF-REF, heart failure with reduced ejection fraction; LLN, lower limit of normal; LVEF; left ventricular ejection fraction; m, months; NA, not available; No., number of patients; NYHA, New York Heart Association;

treatment of HF,[157] a careful timing and interpretation of pulmonary function tests (PFTs) is required to avoid misdiagnosis and inappropriate treatment of COPD.[44] Ideally, PFTs should be used under stable conditions when clinically euvolemic to establish a valid diagnosis of COPD. However, data on the need of serial pulmonary function measurements to confirm persistent airway obstruction and thus COPD are lacking in patients with stable non-congested CHF. It remains therefore unknown whether a confirmatory spirometry is necessary for the correct diagnosis of COPD in patients with stable non-congested CHF.

1.4 Pulmonary function impairment in HF

Isolated or combined pulmonary function abnormalities, such as restriction, diffusion impairment, and to a lesser extent airway obstruction are common in patients with CHF[216-223] (**Table 2**) and can contribute to the perception of dyspnea[224] and exercise intolerance.[224-230] There are only few studies of pulmonary function in patients with acute decompensated HF, most likely due to the difficulty involved in studying these patients.[217] Available data indicates that this group of patients may exhibit obstructive and restrictive pulmonary abnormalities, and to a lesser extent diffusion impairment.[221-223, 231] (**Table 3**) Other abnormalities may also be encountered in patients with HF,

	Men, %	NYHA	LVEF, %	FS/CS, %	Definition of COPD	COPD prevalence, %	Severity of COPD, %	COPD under-/ overdiagnosis, %
	64	III-IV	39 (38-40) #	70	GOLD ≥ 2	35 Diastolic HF: 41 Systolic HF: 31	GOLD II: 51 GOLD III/IV: 39/10	25 / 33
	70	I-III	NA	49	GOLD	39	GOLD I/II: 26/51 GOLD III/IV: 19/4	NA

P, prospective; PY, pack-years; R, retrospective; w, weeks; yr(s), year(s). # Mean (95% confidence interval). ^ Median (interquartile range). * 10 of 40 (24%) patients with both CHF and COPD were aware of airflow limitation and were properly treated. ** 23 of 36 (64%) patients with GOLD-COPD were unaware of having any pulmonary disease. *** Among patients with irreversible airway obstruction according to the LLN criteria, 68% did not report a history of COPD. Among patients without irreversible airway obstruction according to LLN criteria, 6% had a previous diagnosis of COPD. †81% of patients with GOLD-COPD did not have a history of COPD. 4% of patients without GOLD-COPD did have a history of COPD.

such as ventilation-perfusion-mismatch,[220, 224, 232] reduced lung compliance,[221, 224, 233] respiratory muscle weakness,[228, 234-239] bronchial hyperresponsiveness[223, 240-243] hyperventilation at rest and with exercise and expiratory flow limitation (mainly in supine position),[216, 219, 237, 244-248] but lie outside the scope of this thesis.

Reported prevalence rates of pulmonary function abnormalities in patients with CHF vary substantially between 41% and 93% for diffusion impairment, 21-55% for restriction, and 14-60% for airway obstruction (**Table 2**). Corresponding figures are 35%, 17-46%, and 19-61%, respectively, in patients with acute (decompensation of) HF and those hospitalized for HF (**Table 3**).These varying rates across the studies can be partly explained by the usually small number of patients included and differences in study population as well as diagnostic criteria used to define pulmonary function abnormalities. The majority of studies have used conventional cutoff values to define an abnormality, failing to diagnose pulmonary function impairment according to internationally accepted diagnostic criteria.[249] Moreover, some studies described a restrictive lung function defect on the basis of reduced forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) with normal FEV_1/FVC ratio.[250] However, because FEV_1 and FVC may also be proportionately reduced with a normal ratio in patients with severe COPD and gas trapping, the diagnosis of restriction additionally requires detection of reduced total lung capacity (TLC) by

plethysmography. Finally, a large number of studies have included (potential) heart transplant recipients, who represent one extreme of the HF spectrum.[250-256] Therefore, it is less known to what extent CHF patients who do not belong to the most severe category of HF have pulmonary function abnormalities and which of these abnormalities prevail.

Several factors have been implied to play a role in the etiology of pulmonary function impairment in patients with HF, including the effects of HF itself on pulmonary function in addition to (previously undiagnosed) underlying pulmonary disease and confounding influences such as smoking, coronary artery bypass grafting (CABG), and obesity.[216-223, 232, 257]

Diffusion impairment has been thought to be related to the thickening of alveolar-capillary membrane due to hydrostatic mechanical injury, interstitial edema, remodeling, and fibrosis.[216-218, 221] Pressure or volume overload of the lung micro-circulation in HF causes structural adaptations of the alveolar-capillary membrane.[217, 218] In acute HF, hydrostatic mechanical injury can cause breaks and discontinuities in the endothelial and epithelial layers of the blood-gas barrier, the so-called alveolar-capillary stress failure,[258] and impair the cellular pathways involved in fluid filtration and reabsorption.[217, 218] This process, which is generally reversible, leads to resistance to gas transfer.[217, 218] In CHF, in which sustained neurohormonal activation has a significant pathophysiological role, a remodeling process may take place that is characterized by fixed extracellular matrix collagen proliferation. These changes may be protective against edema development on the one hand and may impair diffusing capacity on the other hand.[217, 218, 232] Importantly, the damage caused to the alveolar-capillary membrane in CHF has been suggested to be permanent and may explain why heart transplantation does not affect (or may even worsen) pulmonary diffusing capacity despite an improvement in hemodynamic status and lung volumes.[251-255, 259-266] Also, although ultrafiltration reduces lung fluid content, it does not improve diffusing capacity in CHF.[267] In addition, although cardiac resynchronization therapy increases static and dynamic lung volumes, diffusing capacity for carbon monoxide remains unchanged.[268] Furthermore, a relationship has been established between the time course of HF and extent of gas transfer alterations, suggesting that reversibility of diffusion impairment might depend on the disease time course.[260] However, infusion of saline in patients with CHF is associated with a reduction in diffusing capacity,[269-272] suggesting that abnormal pulmonary diffusion in CHF has a variable component that could be amenable to therapeutic intervention. Indeed, several pharmacological interventions were found to increase diffusing capacity, including spironolactone,[273] ACE-I enalapril,[269, 274-277] and type 5 phosphodiesterase inhibitor sildenafil,[278] while hydralazine-isosorbide dinitrate,[274, 277] ARB losartan,[269, 276]

and non-selective beta-blocker carvedilol[279] did not affect diffusing capacity. Furthermore, aerobic exercise training may also favorably affect gas exchange.[280] Little is known about the effects of other diuretics than spironolactone on diffusing capacity. Treatment for congestive HF did not result in improvement in diffusing capacity in two small studies.[281, 282] On the other hand, diffusing capacity did increase after 1 year of treatment with diuretics and ACE-I/ARBs in 20 patients with newly diagnosed congestive HF.[283] However, 87% of the patients were already taking diuretics prior to the study and therefore the improvement in diffusing capacity may be related to the addition of ACE-I rather than the effect of diuretics.

Other possible causes of diffusion impairment in HF include reduced lung and pulmonary capillary blood volumes, ventilation-perfusion mismatch, recurrent pulmonary emboli, smoking, and cardiopulmonary bypass.[220-222, 257]

Restriction has been linked to cardiomegaly, pleural effusion, respiratory muscle weakness, CABG, fibrosis from chronic congestion, and reduced lung compliance due to chronic vascular engorgement, interstitial/alveolar fluid accumulation, and chronic remodeling of the pulmonary vasculature due to elevated left atrial pressure.[217, 221, 257, 284-286] This restrictive dysfunction generally improves after treatment of HF either by drug therapy,[242, 281, 287] ultrafiltration,[267, 288, 289] or following cardiac transplantation,[252, 255, 261, 264, 290] most likely due to the reduction in lung water and cardiac size. However, other studies could not demonstrate significant improvement in lung volumes after pharmacological treatment for HF[231, 283] or following cardiac transplantation.[254, 291]

Airway obstruction in HF has been attributed to alveolar fluid accumulation, bronchial mucosal swelling, peribronchial edema and fibrosis, squamous metaplasia of bronchial epithelial cells induces by transforming growth factor-ß from the failing heart, geometric decrease in airway size from reduction in lung volume, abnormalities of autonomic control, neurohumoral bronchoconstriction, bronchial hyperresponsiveness, and smoking.[220-223, 257, 292] Airway obstruction generally improves following treatment for HF,[231, 287, 293] although not all studies could confirm this.[242, 281] In addition, treatment directed at reversing airway obstruction with bronchodilators may have an additional role in the management of HF. There are, however, only few studies concerning the beneficial effects of bronchodilators in patients with HF. Improvements in pulmonary function,[106, 293-298] dyspnea,[296] and exercise performance[298] have been reported. Some investigators have even observed an increase of mean FEV_1 greater than 200 mL and 12% in patients with HF,[293-295] especially in those with airway obstruction,[295] LVSD,[294] and during acute decompensation of HF.[293] However, contrasting results have also been published. In the study of Witte et al.[296] nebulized salbutamol (5 mg) and ipratropium bromide (0.5 mg) reduced peripheral airways

Table 2 Prevalence of pulmonary function abnormalities in patients with CHF.

Author, Yr	No.	Population	Exclusion of pulmonary disease	Age, yrs	Men, %	
Khan et al., 2000[295]	25	Symptomatic chronic CoHF, all had a history of repeated hospital admissions	Overt pulmonary disease, bronchial asthma, COPD or history of bronchodilator usage	42 ± 2†	68	
Ewert et al., 1999[251]	56	CHF, heart transplant recipients	History of smoking, pulmonary interstitial disease on X-ray	50 ± 14	84	
Evans et al., 1996[240]	37	Stable CHF, LVSD, no change in medication <1m, CTR > 0.5, limited exercise by breathlessness or fatigue, none had radiological pulmonary edema	A history of asthma, chronic airflow limitation, or bronchodilator usage, recent respiratory infection	61 ± 8	81	
Bussières et al., 1995[252]	14	Male patients undergoing cardiac transplantation and surviving the 1st year	Severe chronic obstructive lung disease or bronchodilator agents	47 ± 12	100	
Egan et al., 1993[254]	22	Cardiac transplant recipients, severe CoHF	NA	50 (17-60)^	95	
Niset et al., 1993[255]	47	Severe chronic CoHF (heart transplant recipients) in a compensated state, receiving maximal medical therapy	NA	49 (17-63)^	89	
Ohar et al., 1993[253]	22	Cardiac transplant recipients, abstinence from tobacco products for at least 2m	NA	53 ± 2†	77	
Naum et al., 1992[250]	56	Chronic severe CMP preceding cardiac transplantation, clinically stabilized and therapeutic regimen optimized before testing	NA	49 ± 11	73	
Wright et al., 1990[256]	132	Potential heart transplant recipients (severe chronic CoHF), inpatients	NA	51 (25-68)^	80	

	NYHA	LVEF, %	FS/CS, %	Definition			Prevalence, %		
				O	R	D	O	R	D
	II-IV	NA	44	ATS (1991)	ATS (1991)	NA	60	40	NA
	NA	NA	0	$FEV_1/VC < 0.75$ $RV/TLC > 120\%$	$VC < 80\%$ $TLC < 80\%$	$DLCO < 80\%$ $KCO < 80\%$	41, 43* 43, 29*	43, 36* 27, 21*	46, 95* 59, 96*
	II-IV	NA	78	$FEV_1/FVC < 0.7$	NA	NA	30	NA	NA
	NA	NA	71	$FEV_1/FVC < 0.7$	$TLC < 75\%$	$TLCOc < 75\%$	14	21	93
	III-IV	NA	86	NA	NA	$DCOc < 80\%$ $KCOc < 80\%$	NA	NA	41 (?) 23
	III-IV	18 ± 9	74	$FEV_1/VC < 0.7$	NA	$KCOc < 75\%$	28 21*	NA	2/3rd
	NA	23 ± 2†	59	$FEV_1/FVC < 0.7$	$TLC < 80\%$	$DCOc < 80\%$	36 27*	55 45*	73 86*
	III-IV	18 ± 10	86	$FEV_1/FVC < 0.7$	$FVC < 80\%$ with $FEV_1/FVC \geq 0.7$	$DLCO < 80\%$	21**	54	64
	Most III-IV	19 ± 7	83	$FEV_1/FVC < 0.7$	$TLC < 80\%$	$DCOc < 75\%$, provided DCO/VA was < predicted	20	33	67

Table 2 Continued.

Author, Yr	No.	Population	Exclusion of pulmonary disease	Age, yrs	Men, %	
Eichacker et al., 1988[304]	9	Chronic CoHF, hemodynamically stable, PCWP ≥ 20 mmHg	A history of asthma	77 ± 7	NA	

Data are presented as mean ± SD and percentages unless stated otherwise. Abbreviations: ATS, American Thoracic Society; CHF, chronic heart failure; CMP, cardiomyopathy; CoHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CS, current smokers; CTR, cardiothoracic ratio; D, diffusion impairment; DLCO(c), diffusing capacity of the lung for carbon monoxide (corrected for hemoglobin concentration); FEV_1, forced expiratory volume in 1 second; FS; former smokers; (F)VC, (forced) vital capacity; KCO(c), transfer coefficient for carbon monoxide (corrected for hemoglobin concentration); LVEF; left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; m, months;

resistance and breathlessness during exercise in twelve patients with stable CHF and increased measures of compliance. However, spirometry was not altered significantly and exercise capacity did not improve with bronchodilation. Similarly, treatment with three weeks of salbutamol (slow-release 8 mg twice daily) did not improve exercise capacity or spirometric measurements in a RCT of twelve CHF patients, although respiratory muscle strength did increase.[299] Furthermore, there were no improvements in symptom scores as measured with the Minnesota living with HF questionnaire and fatigue dyspnea index in the same study. In addition, pre-treatment with nebulized albuterol (2.5 mg) and ipratropium bromide (0.5 mg) had only minor effects on spirometric values at rest and did not influence exercise performance and visual analogue score for dyspnea at peak exercise in a randomized, double-blind crossover study of nine patients with HF.[300] Furthermore, although a small but significant increase in maximal exercise capacity and spirometric indices was seen after pre-treatment with nebulized salbutamol (5 mg) and with ipratropium bromide (0.5 mg) in a randomized double-blind study of ten patients with CHF, both bronchodilators had no effect on the perception of dypnea, as measured by a visual analogue scale.[298] Finally, significant reversibility, defined as more than 400 mL increase in FEV_1 after inhalation of 0.2 mg fenoterol and 40 μg ipratropium, could not be demonstrated in 131 patients admitted with HF in a prospective substudy,[211] whereas only four of eighteen patients with congestive HF had greater than 10% improvement in FEV_1 after bronchodilation in another study.[281] Contrasting results across the studies might be attributed to the small number of patients studied and to the differences in study population, bronchodilators used, and definition of bronchodilator responsiveness (BDR).

NYHA	LVEF, %	FS/CS, %	Definition			Prevalence, %		
			O	R	D	O	R	D
IV	24 ± 6	56	$FEV_1/FVC <$ 0.75	NA	NA	33	NA	NA

NA, not available; No., number of patients; NYHA, New York Heart Association; O, airway obstruction; PCWP, pulmonary capillary wedge pressure; R, restriction; RV, residual volume; TLC, total lung capacity; TLCO(c), transfer factor of the lung for carbon monoxide (corrected for hemoglobin concentration); VA, alveolar volume; yr(s), year(s). † Standard error (SE). ^ Mean (range). * After heart transplantation. ** Isolated forced expiratory flow $(FEF)_{25-75}$ reduction (FVC ≥ 80% pred., $FEV_1/FVC \geq 0.7$, $FEF_{25-75} <$ 60% pred.) = 3.6%.

Besides the possible etiological factors mentioned above, it should also be considered that other conditions may also be related to pulmonary function impairment in patients with HF, such as previously undiagnosed pulmonary disease. In fact, COPD is frequently unrecognized in patients with HF (**Table 1**). A careful evaluation of the patient and potential treatment options is therefore necessary before ascribing pulmonary function impairment only to the effects of HF.

Irrespective of the causes, pulmonary function abnormalities associated with CHF may explain part of the symptoms and functional disability encountered in these patients.[224-230, 244] Moreover, pulmonary function impairment increases with the severity of HF,[228, 229, 301] provides important prognostic information,[213, 214, 302, 303] and may ameliorate or normalize with several treatment modalities, such as pharmacological and non-pharmacological treatment of HF and anti-obstructive therapy with bronchodilators as mentioned above. Pulmonary function might thus be used as a guide for the evaluation of patients with CHF, with respect to severity of disease, prognosis, and response to treatment. Therefore, it is of great importance to have adequate knowledge regarding the occurrence of these pulmonary function abnormalities in patients with HF.

Table 3 Prevalence of pulmonary function abnormalities in patients with acute (decompensation of) HF or hospitalization for HF.

Author, Yr	No.	Population	Exclusion of pulmonary disease	Age, yrs	Men, %	
Brenner et al., 2013[157]	272	Hospitalized for CoHF with LVEF ≤ 40%	History of bronchial asthma	66 ± 12	80	
Miniati et al., 2013[213]	260	Hospitalized for systolic HF (LVEF < 50%), evaluation under stable clinical conditions shortly before hospital discharge	Active cancer, pulmonary arterial hypertension	68 (58-75)^	80	
Miniati et al., 2013[214]	439	Hospitalized for systolic HF (LVEF < 50%), evaluation under stable clinical conditions shortly before hospital discharge	Active cancer	68 (? - ?)^	79	
Boni et al., 2005[245]	9	Acute left HF (inpatients), systolic or diastolic, nonobese, NS	COPD, bronchodilators, corticosteroids, antibiotics	77 ± 7	22	
Faggiano et al., 1993[287]	13	Severe chronic CoHF (admitted), LVEF < 30%, no BB agents, physical findings of pulmonary and systemic congestion without acute pulmonary edema and/or pleural effusion	History of smoking or lung disease	59 ± 10	100	
Siegel et al., 1990[305]	34	CoHF with LVEF < 40%, 13 admitted with CoHF, 21 with known CoHF evaluated for chronic arrhythmias	Pneumonia, pleural effusion, overt pulmonary edema, underlying lung disease, clinical or radiographic evidence of neoplasm, previous lung resection or a history of drugs that could result in pulmonary toxicity	65 ± 10	71	
Pison et al., 1989[242]	12	Chronic left HF during acute decompensation and after intensive diuretic treatment, hemodynamically stable, none with BB, 8 subjects with signs of right HF	NA	60 ± 10	83	

	NYHA	LVEF, %	FS/CS, %	Definition			Prevalence, %		
				O	R	D	O	R	D
	II-IV	32 ± 8	58	Post-BD FEV_1/FVC < 0.7	NA	NA	19*	NA	NA
	III/IV 32%	32 (25-40)^	CS: 19	-	FEV_1/SVC > 5th percentile, TLC < 5th percentile of predicted	NA	-	20	NA
	NA	NA	NA	-	FEV_1/SVC > 5th percentile, TLC < 5th percentile of predicted	NA	-	19	NA
	NA	43 ± 15	0	NA**	NA**	NA	44**	22**	NA
	IV	NA	NA	ATS (1981)	ATS (1981)	NA	46***	46***	NA
	NA	25 ± 7	100	NA	NA	Diffusing capacity corrected for hemoglobin < lower 95 confidence limit	NA	NA	35
	III-IV	NA	100	FEV_1 ≤ 80% and FEV_1/FVC < 85% pred.	Significantly reduced TLC, VC, and FRC	NA	50 25†	17 8†	NA

Table 3 Continued.

Author, Yr	No.	Population	Exclusion of pulmonary disease	Age, yrs	Men, %	
Light and George, 1983[281]	28	Admitted with CoHF, most with both right and left HF	History of chronic obstructive lung disease	62 ± ?	71	

Data are presented as mean ± standard deviation (SD) and percentages unless stated otherwise. Abbreviations: ATS, American Thoracic Society; BB, beta-blockers; CoHF, congestive heart failure; CS, current smokers; D, diffusion impairment; FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FS; former smokers; FVC, forced vital capacity; HF, heart failure; LVEF; left ventricular ejection fraction; NA, not available; No., number of patients; NS, non-smokers; NYHA, New York Heart Association; O, airway obstruction; post-BD, post-bronchodilator; R, restriction; SEE, standard error of the estimate; SVC, slow vital capacity; TLC, total lung capacity; yr(s), year(s). ^ Median

1.5 Different definitions of COPD and pulmonary function impairment: the lower limit of normal versus conventional cutoff values

As mentioned before, spirometry is required for the diagnosis of COPD by measuring persistent airflow limitation. However, there is still no consensus on the most appropriate threshold of FEV_1/FVC for diagnosing airflow limitation.[10-20] The GOLD guidelines recommend the use of the fixed ratio of $FEV_1/FVC < 0.70$ for the sake of simplicity.[1] However, a growing body of literature indicates that considering the physiological decline of the FEV_1/FVC ratio with age (the FEV_1 declines more rapidly with age than the FVC in normal subjects) the use of the fixed ratio may lead to overdiagnosis of COPD in elderly subjects[5, 306-321] and underdiagnosis of COPD in young adults.[314-323] To avoid misclassification, the American Thoracic Society/European Respiratory Society (ATS/ERS) recommends the use of statistically derived LLN values for FEV_1/VC that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal.[249] This is particularly important in patients with HF, given that HF is most prevalent among elderly individuals.[32] Thus, previously reported COPD prevalence rates may have been overestimated in prior studies that have used the fixed ratio of 0.7 to define COPD in patients with HF (**Table 1**). Although population-based studies have shown that the application of different criteria to define airflow obstruction dramatically changes the prevalence of COPD,[5, 309, 310, 324-327] it is less well understood to what extent this occurs in patients with HF.[169, 215]

NYHA	LVEF, %	FS/CS, %	Definition			Prevalence, %		
			O	R	D	O	R	D
NA	NA	46	FEV_1/FVC outside normal range (pred-1.65 SEE)	NA	NA	61‡	NA	NA#

(interquartile range). * Airway obstruction had resolved in 48% of patients 6 months after discharge. ** No definition for pulmonary function impairment was provided in the article. Prevalence data were extracted using the following definitions: airway obstruction, $FEV_1/FVC < 0.7$; restriction, $FVC < 80\%$ predicted with $FEV_1/FVC \geq 0.7$. *** Isolated airway obstruction: 31%; isolated restriction: 31%; mixed pulmonary function abnormalities: 15%. † After treatment for HF. ‡ Both during initial assessment and at the time that the pulmonary function of the patients was the best. # Mean diffusing capacity for carbon monoxide was within normal range.

An incorrect diagnosis of COPD may result in unnecessary treatment for COPD with possible side-effects and adverse cardiovascular events associated with pharmacological treatment for COPD and undertreatment with life-saving beta-blockers.[12, 81, 82] Moreover, an incorrect diagnosis and interventions for COPD may have a considerable psychological impact on the subject and his/her family and may lead to unnecessary costs.[12] Conversely, misclassifying a number of young adults already affected by COPD as healthy, prevents early interventions that could limit disease progression. Therefore, there is a need for clear diagnostic criteria for COPD to avoid diagnostic confusion, incorrect diagnosis, and inappropriate treatment.

PFTs are also used for the diagnosis of other pulmonary function abnormalities than airflow limitation, such as diffusion impairment and restriction. Similarly, there is no consensus on how to define these pulmonary function abnormalities. Traditionally, the 80% predicted value (i.e. diffusing capacity or TLC < 80% predicted) has been used. This frequently used 80% predicted value has, however, neither statistical nor physiological validity[249, 328] and may misclassify more than 20% of patients leading to false-positive diagnosis in the elderly and underdiagnosis in younger patients.[314] Limits of normal as the predicted ± 20% can only be accurate when the variance above and below the predicted regression line is proportional with the predicted value (i.e. heteroscedastic: large variance with large values and small variance with small values).[314, 328] However, since this is not the case, as the scatter around the predicted regression line is constant (homoscedastic) in pulmonary function measurements, the 80% predicted rule of thumb may lead to false-positive diagnosis in the elderly and shorter individuals with smaller predicted values and underdiagnosis

in younger and taller patients with larger predicted values.[314, 328] Misinterpretation of PFT results may lead to incorrect diagnosis of disease in elderly patients with HF and as a consequence unnecessary treatment. Moreover, results may be interpreted as having more severe or unstable HF due to the effects of HF on pulmonary function and as a result unnecessary intensified treatment for HF. Finally, misdiagnosis may interfere with interpretation of research aiming to understand the impact of HF and several clinical variables on pulmonary function.[329, 330] To avoid misclassification, ATS/ERS guidelines[249] again recommend the use of the fifth percentile LLN values, which are calculated by subtracting 1.64 times the residual standard deviation (RSD) from the predicted value. However, studies using the LLN values to assess the prevalence of pulmonary function abnormalities and their predictors in patients with HF are lacking.

1.6 Outline of this thesis

Given the gaps in current knowledge as described in the general introduction, the aim of this thesis is to provide more insight in the occurrence of COPD and pulmonary function abnormalities using different definitions in patients with CHF.

The main objectives of this thesis are:

1. To determine the prevalence of COPD in patients with CHF according to two definitions of airflow obstruction: the LLN versus the fixed ratio of $FEV_1/FVC < 0.70$.

2. To assess the extent of underdiagnosis and overdiagnosis of COPD in patients with CHF.

3. To examine whether serial PFTs are necessary for the correct diagnosis of COPD in patients with stable non-congested CHF.

4. To determine the prevalence of pulmonary function abnormalities in patients with CHF according to recent ATS/ERS guidelines using the LLN compared to conventional cutoff values.

5. To assess predictors of pulmonary function impairment in patients with CHF according to the LLN in comparison to conventional cutoff values.

6. To evaluate the effect of inhaled bronchodilators on pulmonary function and dyspnea in patients with CHF.

After a general introduction in **chapter 1**, the **2nd chapter** of this thesis describes the prevalence of COPD, including over- and underdiagnosis of COPD, in patients with CHF according to the widely used GOLD criteria. In addition, it provides an answer to the question whether serial PFTs are necessary for the correct diagnosis of COPD in patients with stable non-congested CHF. **Chapter 3** compares two definitions of airflow limitation, namely the LLN versus the fixed ratio of $FEV_1/FVC < 0.70$, regarding the prevalence of COPD in patients with CHF. **Chapter 4** provides prevalence rates of pulmonary function abnormalities in patients with CHF according to the LLN versus conventional cutoff values. **Chapter 5** describes several predictors of these pulmonary function abnormalities and the effect of using different diagnostic criteria, namely the LLN versus the conventional cutoff values. **Chapter 6** evaluates the effect of inhaled bronchodilators on pulmonary function and dyspnea in patients with CHF. Finally, **chapters 7** and **8** of this thesis provide a summary and discussion of all studies and the main findings. Subsequently, a perspective on the future is provided.

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CHAPTER 2

Serial pulmonary function tests to diagnose COPD in chronic heart failure

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Abstract

Background: It is unknown whether serial pulmonary function tests are necessary for the correct diagnosis of chronic obstructive pulmonary disease (COPD) in patients with stable non-congested chronic heart failure (CHF). The aim of this study was to determine the prevalence of COPD in outpatients with stable CHF without pulmonary congestion using initial as well as confirmatory spirometry three months after treatment for COPD.

Methods: Spirometry was performed in 187 outpatients with stable CHF without pulmonary congestion on chest radiograph who had a left ventricular ejection fraction $< 40\%$ (mean age 69 ± 10 years, 78% men). COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease guidelines. The diagnosis of COPD was confirmed three months after treatment with tiotropium in newly diagnosed COPD patients.

Results: Using a three month follow-up spirometry to confirm initial diagnosis of de novo COPD did not change COPD prevalence significantly: 32.6% initially versus 32.1% after three months of follow-up. Only 1 of 25 (4%) patients with newly diagnosed COPD was not reproducibly obstructed at follow-up. COPD was greatly under- (19%) and overdiagnosed (32%).

Conclusions: Spirometry should be used under stable and euvolemic conditions to decrease the burden of undiagnosed or overdiagnosed COPD in patients with CHF. Under these conditions, a confirmatory spirometry is unnecessary, as it does not change a newly established diagnosis of COPD in the vast majority of patients with CHF.

Keywords: chronic obstructive pulmonary disease, chronic heart failure, prevalence, serial pulmonary function tests, underdiagnosis, overdiagnosis.

Background

Heart failure (HF) is a common clinical condition with high mortality and morbidity rates.[1] Chronic obstructive pulmonary disease (COPD) frequently coexists with HF, leading to poor prognosis as well as diagnostic and therapeutic challenges.[2-17] Estimates of COPD prevalence in patients with HF vary substantially between 9% and 52% in earlier reports that relied on clinical data, disease codes, or self-reported COPD for establishing the diagnosis.[2] Spirometry is considered to be the gold standard for the diagnosis of COPD,[18] but is unfortunately still underutilised.[19] Studies that used spirometry have also reported varying prevalence rates of COPD (9 - 44%) depending on study design, population, and diagnostic criteria.[14-17, 20-23] Airway obstruction is a dynamic phenomenon in HF, as it may be present in congestive HF and may disappear with treatment of HF.[14] Therefore, a careful timing and interpretation of pulmonary function tests (PFTs) is required to avoid misdiagnosis and inappropriate treatment.[2] Ideally, serial PFTs should be used under stable conditions when clinically euvolemic to establish a valid diagnosis of COPD by confirming persistent airway obstruction. However, data on the need of serial pulmonary function measurements are scarce and even lacking in patients with stable chronic HF (CHF). It is therefore unknown whether a confirmatory spirometry is necessary for the correct diagnosis of COPD in patients with stable non-congested CHF.

The present study determined the prevalence of COPD in outpatients with stable CHF without pulmonary congestion using initial as well as confirmatory spirometry three months after treatment with tiotropium in patients with newly diagnosed COPD.

Methods

Study design and participants

All patients attending two outpatient cardiology departments of a large general hospital in The Netherlands were screened for inclusion in this prospective study between October 2009 and December 2010. In addition, existing patient lists were used to ensure that the majority of HF population had been examined for eligibility. Inclusion criteria were CHF[1] with left ventricular ejection fraction (LVEF) $< 40\%$, New York Heart Association (NYHA) class I-IV, and age of ≥ 18 years. CHF was defined according to European Society of Cardiology guidelines.[1] Echocardiography was performed in patients without a recent (≤ 6 months) echocardiography to confirm persisting left ventricular systolic dysfunction (LVSD). Patients were classified as having stable HF in the absence of hospitalization due to progression of HF within 3 months, change in diuretics within 1 month, 3% or more weight gain within 3 days,

and more than 50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) within 1 month when the baseline NT-pro-BNP was 100 pmol/L or higher or more than 100 pmol/L increase of NT-pro-BNP within 1 month when baseline NT-pro-BNP was below 100 pmol/L.[24] Pulmonary congestion was evaluated on standard posterior-anterior and lateral chest radiographs for the presence or absence of alveolar edema, pleural effusion, Kerley-B lines, and/or the redistribution of pulmonary blood flow by independent radiologists who qualitatively assessed the chest radiographs with an overall clinical impression. We excluded patients who were not able to cooperate or undergo spirometry or who had asthma according to their medical chart. Other exclusion criteria were malignancy with a poor prognosis (survival $<$ 6 months) and participation in another cardiology study. Patients who had been hospitalized in the pulmonary department in the past six weeks were included six weeks after discharge to ensure that their pulmonary function was stable at the time of spirometry testing.

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP according to the standard methods used at the hospital laboratory. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including height and weight measurement, spirometry, and a chest radiograph. In addition, a second blood sample (NT-pro-BNP) was taken to determine the stability of HF. The Minnesota Living with Heart Failure Questionnaire,[25] modified Medical Research Council dyspnea scale,[26] and 10-point Borg score[27] were used to evaluate quality of life, effect of breathlessness on daily activities, and dyspnea at rest, respectively. Additional data were collected from medical records and personal interviews. Arterial blood gas analysis was carried out in patients with severe airway obstruction to determine whether they had chronic respiratory failure.[18]

Patients with newly diagnosed COPD were followed up three months after standard treatment for COPD with once-daily 18 μg tiotropium. A third blood sample (NT-pro-BNP) was taken and spirometry was repeated to confirm persistent airway obstruction characteristic of COPD and exclude asthma as much as possible. Thus only patients with persistent airway obstruction on three months of follow-up were classified as having COPD.

Spirometry testing

Spirometry (MasterLab Pro; Jaeger; Würzburg, Germany) was performed by trained and certified operators using standard techniques and according to European Respiratory Society standards for acceptability and reproducibility.[28] The reference values of the European Community for Coal and Steel were used.[28] Subjects with airway obstruction underwent post-bronchodilator spirometry 30 minutes after

inhalation of four doses of 100 μg aerosolised salbutamol and four doses of 20 μg aerosolised ipratropium via Volumatic spacer. Participants were instructed not to take bronchodilators 6-24 hours before the tests, depending on the type of bronchodilator used. At follow-up, salbutamol and ipratropium were used, as previously described, when patients discontinued the use of tiotropium > 24 hours prior to spirometry. Care was taken to match the timing of the second spirometry testing to the first to reduce variations that may occur over a 24-hour period.

Definitions

COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines as post-bronchodilator ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) < 0.7.[18] *COPD severity staging* was determined on the basis of FEV_1 percent predicted according to GOLD criteria: FEV_1 ≥ 80% predicted (stage I, mild), 50% ≤ FEV_1 < 80% predicted (stage II, moderate), 30% ≤ FEV_1 < 50% predicted (stage III, severe), and FEV_1 < 30% predicted or FEV_1 < 50% predicted plus chronic respiratory failure (stage IV, very severe).[18]

Smoking status was defined as never (< 100 cigarettes in a lifetime), former (≥ 3 months ago), or current smoker (< 3 months). *Smoking pack-years (PY)* were based only on the tobacco cigarette history and one PY was defined as smoking 20 cigarettes a day for 1 year.

Dyspnea was defined as resting dyspnea or dyspnea at any level of exertion, *chronic cough* as cough ≥ 3 months prior to the study, *chronic sputum production* as regular production of sputum for ≥ 3 months in 2 consecutive years, and *aspecific bronchial hyperreactivity (ABHR)* as respiratory symptoms in response to perfumes, scent of baking or paint, fog, cold air, or temperature changes.

Ethical considerations

The study was approved by the regional Research Ethics Committee Arnhem-Nijmegen in The Netherlands (2009/101, NL27798.091.09, ClinicalTrials.gov Identifier NCT01429376) and complies with the Declaration of Helsinki. All participants gave written informed consent.

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD) or as number (%). Baseline characteristics of patients with and without COPD were compared using the independent t-test or Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate. Correlations between COPD and LVEF and between COPD and NT-pro-BNP were examined using the

Pearson's and Spearman's correlation coefficient tests, respectively. Association between COPD and NYHA class was examined using the chi-square test. Statistical analyses were performed using the Statistical Package for Social Science (SPSS, version 15.0). All statistical tests were two-sided and a p-value < 0.05 was considered significant.

Results

Patient characteristics

After screening of the entire HF population, a cohort of 337 patients with CHF was initially enrolled in this study. Thirty-eight patients withdrew informed consent and 65 patients were excluded due to several other reasons as specified in Figure 1. The remaining 234 patients were finally included of whom 187 had stable CHF without signs of pulmonary congestion. The characteristics of these patients are shown in Tables 1 and 2. Mean age and LVEF were 69 $\pm$ 10 years and 29 $\pm$ 7%, respectively, and 78% were men. The majority of patients (72%) had NYHA class II, while only 16% and 12% had NYHA class I and III/IV, respectively. Almost 60% had an ischemic etiology of HF. Other causes of HF were idiopathic (24%), hypertension (6%), valve disease (6%), tachycardiomyopathy (3%), and other (2%). Most patients were former or current smokers (83%) and reported symptoms of dyspnea (82%). Other respiratory symptoms were less common (cough 36%, sputum 23%, ABHR 29%). The patients received optimized, individually tailored drug treatment as maintenance therapy for their CHF.

COPD prevalence

Initially, 61 (32.6%) CHF patients were diagnosed with COPD based on spirometry of whom 34 had a history of obstructive lung disease (OLD). Subsequently, 27 patients with newly diagnosed COPD were followed up three months after standard treatment for COPD. Two patients were lost to follow-up; one deceased and the other withdrew informed consent. One of the remaining 25 patients no longer had airway obstruction at follow-up, which was classified as mild upon initial assessment. Thus, COPD prevalence was 32.1% [25.4-38.8%] after three months of follow-up.

COPD prevalence tended to be higher in men than women ($p = 0.051$). It was also higher in former (36%) and current smokers (43%) than in non-smokers (9%), with no significant differences between current and former smokers (Figure 2A). None of the 9 patients aged between 31 and 50 years were diagnosed with COPD. COPD prevalence according to other age categories is shown in Figure 2B. Most patients had mild (46.7%) or moderate (40.0%) COPD, while only 8.3% and 5.0% had severe or very severe COPD, respectively.

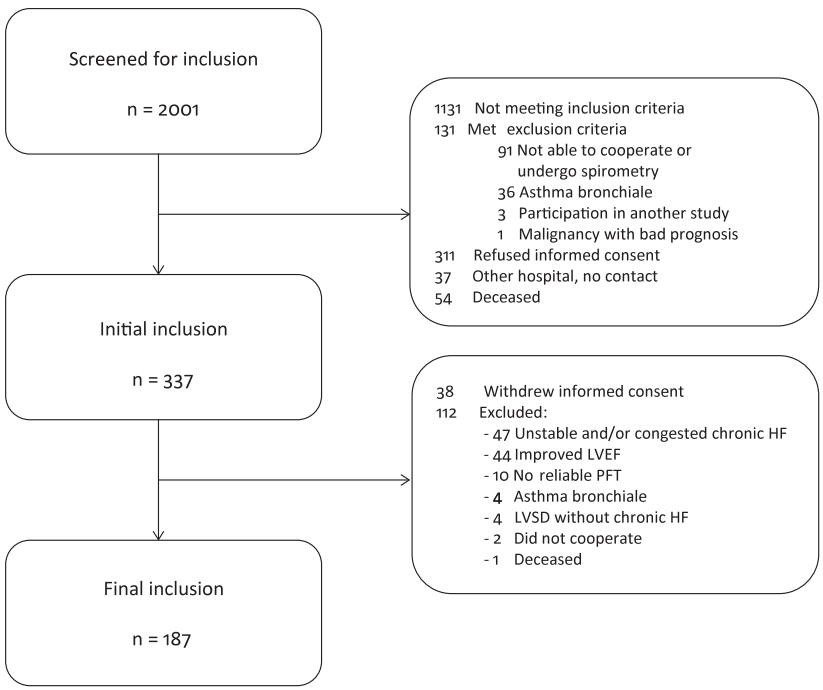

Figure 1 Flow-diagram of screening and final inclusion of study participants. Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; PFT, pulmonary function tests.

Underdiagnosis and overdiagnosis of COPD

COPD was both over- and underdiagnosed (Figure 2 and Table 3). In terms of overdiagnosis, 32% (16/50) of patients with a history of OLD failed to demonstrate airway obstruction. In terms of underdiagnosis, 19% (26/137) of patients without a history of OLD were newly diagnosed with COPD based on spirometry. A history of OLD was defined as COPD (n = 43) or not further specified airway obstruction (n = 7) based on patient charts and/or general practitioner diagnosis.

Determinants of COPD

Table 1 shows characteristics of patients with and without COPD based on spirometry. Pulmonary symptoms and the results of questionnaires, laboratory tests, and spirometry are presented in Table 2. In univariate analysis patients with COPD were generally men who smoked more, used more pulmonary medication, had more respiratory symptoms of cough, ABHR, and dyspnea according to Borg score, and

Table 1 Characteristics of patients with and without COPD based on spirometry.

	All (n = 187)	No COPD (n = 127)	COPD (n = 60)	p-value
Age, years	69 ± 10	68 ± 11	70 ± 9	0.173
Male sex, n (%)	146 (78)	94 (74)	52 (87)	0.051
BMI, kg/m^2	28 ± 5	29 ± 5	28 ± 5	0.064
LVEF, %	29 ± 7	29 ± 7	29 ± 7	0.401
NYHA class, %				
NYHA I-II	164 (88)	114 (90)	50 (83)	0.211
NYHA III-IV	23 (12)	13 (10)	10 (17)	0.211
Ischemic etiology	110 (59)	71 (56)	39 (65)	0.238
Smoking history, n (%)				0.008
Non-smoker	32 (17)	29 (23)	3 (5)	
Current smoker	23 (12)	13 (10)	10 (17)	
Former smoker	132 (71)	85 (67)	47 (78)	
PY, years	24 ± 24	21 ± 21	30 ± 28	0.016
Co-morbidity, n (%)				
Myocardial infarction	109 (58)	71 (56)	38 (63)	0.336
Atrial fibrillation	54 (29)	38 (30)	16 (27)	0.647
Hypertension	80 (43)	51 (40)	29 (48)	0.291
Diabetes mellitus	46 (25)	33 (26)	13 (22)	0.522
PCI/CABG	76 (41)	48 (38)	28 (47)	0.249
CRT/ICD	64 (34)	49 (39)	15 (25)	0.068
Medication, n (%)				
ACE-I/ARB	174 (93)	119 (94)	55 (92)	0.759
β-blockers	172 (92)	116 (91)	56 (93)	0.778
Selective	99 (58)	66 (57)	33 (59)	0.801
Non-selective	73 (42)	50 (43)	23 (41)	0.801
Diuretics	159 (85)	107 (84)	52 (87)	0.666
Aldosterone-antagonists	65 (35)	47 (37)	18 (30)	0.348
ICS/OCS	26 (14)	9 (7)	17 (28)	0.000
β-agonists	29 (16)	7 (6)	22 (37)	0.000
Anticholinergics	29 (16)	6 (5)	23 (38)	0.000

Data are presented as mean ± SD and number (%). Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; ICS/OCS, inhalation/oral corticosteroids; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; PY, pack-years.

tended to have a lower body mass index. In addition, they had worse lung function test results except for FVC. Other variables studied did not significantly vary between patients with and without COPD based on spirometry.

COPD was not associated with a higher NYHA class ($p = 0.130$). Also, there were no significant correlations between COPD and LVEF ($p = 0.401$) or NT-pro-BNP ($p = 0.251$).

Table 2 Pulmonary symptoms and results of questionnaires, laboratory tests, and spirometry of patients with and without COPD based on spirometry.

	All (n = 187)	No COPD (n = 127)	COPD (n = 60)	p-value
Symptoms, n (%)				
Cough	67 (36)	38 (30)	29 (48)	0.014
Sputum	43 (23)	26 (20)	17 (28)	0.233
Dyspnea	153 (82)	101 (80)	52 (87)	0.237
ABHR	55 (29)	29 (23)	26 (43)	0.004
Questionnaires				
MLHFQ	20 ± 17	19 ± 17	21 ± 18	0.568
MRC	1.5 ± 1.3	1.4 ± 1.3	1.7 ± 1.4	0.149
Borg	0.9 ± 1.2	0.8 ± 1.2	1.1 ± 1.3	0.036
Laboratory data				
NT-pro-BNP1, pmol/L	201 ± 289	184 ± 273	236 ± 321	0.290
NT-pro-BNP2, pmol/L	198 ± 308	179 ± 289	239 ± 345	0.250
Spirometry				
FEV_1, L	2.5 ± 0.8	2.7 ± 0.8	2.1 ± 0.7	0.000
FEV_1, % predicted	88 ± 21	96 ± 15	72 ± 22	0.000
FVC, L	3.7 ± 1.0	3.7 ± 1.0	3.8 ± 1.0	0.699
FVC, % predicted	102 ± 19	102 ± 17	101 ± 23	0.602
FEV_1/FVC, %	68 ± 11	74 ± 5	55 ± 10	0.000

Data are presented as mean ± SD and number (%). Only pre-bronchodilator lung function test results are presented to make comparison between groups possible. Laboratory data 1 and 2 refer to first (at baseline) and second (one month later) blood samples, respectively. Abbreviations: ABHR, aspecific bronchial hyperreactivity; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, ratio of forced expiratory volume in one second to forced vital capacity; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRC, modified Medical Research Council dyspnea scale; NT-pro-BNP, N-terminal pro-B natriuretic peptide.

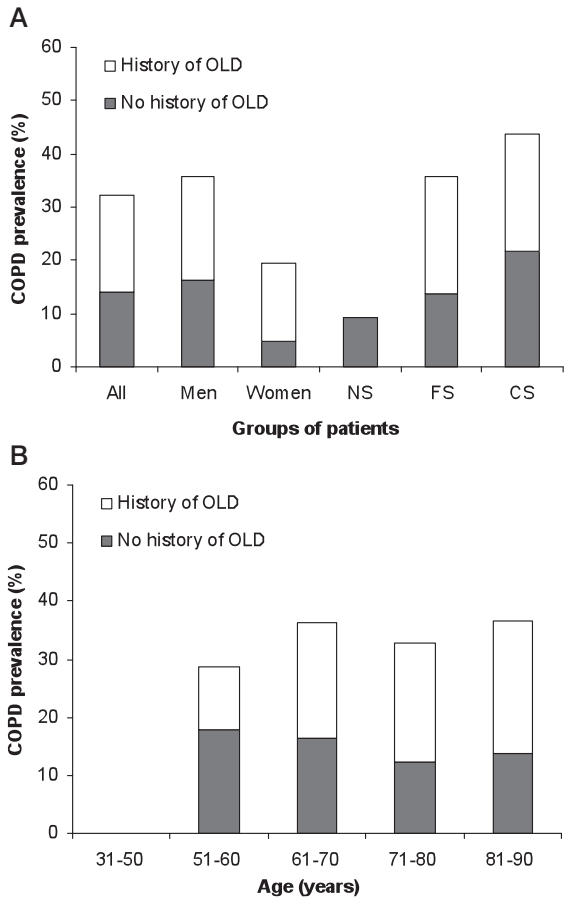

Figure 2 COPD prevalence and underdiagnosis according to (**A**) gender and smoking status, and (**B**) age categories. Abbreviations: COPD, chronic obstructive pulmonary disease; CS, current smokers; FS, former smokers; NS, non-smokers; OLD, obstructive lung disease. The grey parts of the bar represent the proportion of patients with COPD based on spirometry who did not have a history of OLD (i.e. previously underdiagnosed patients).

Table 3 Underdiagnosis and overdiagnosis of COPD.

	COPD (+)	COPD (-)	Total
History of OLD (+)	34 (18.2)	16 (8.6)	50 (26.7)
History of OLD (-)	26 (13.9)	111 (59.4)	137 (73.3)
Total	60 (32.1)	127 (67.9)	187 (100)

Data are presented as number (%). Abbreviations: COPD, chronic obstructive pulmonary disease; OLD, obstructive lung disease.

Discussion

We observed a high prevalence (32.1%) of COPD in a well defined subgroup of stable CHF patients without pulmonary congestion who were recruited from two outpatient cardiology departments of a large general hospital. Using a three month follow-up spirometry to confirm initial diagnosis of de novo COPD did not change COPD prevalence significantly. The majority of patients remained obstructive at follow-up after three months of treatment with tiotropium.

Contrary to our results, initial airway obstruction was found in 19% of patients hospitalized for congestive systolic HF in the study of Brenner et al.,[14] but had resolved in 47% of these patients six months after discharge. This indicates that airway obstruction is a dynamic phenomenon in patients with HF, which often resolves after re-compensation. Therefore, a careful timing and interpretation of PFTs is required to avoid misdiagnosis and inappropriate treatment.[2] Ideally, lung function measurements should be obtained under stable conditions when clinically euvolemic to establish a valid diagnosis of COPD. Indeed, the vast majority of patients, except for one (4%), with stable CHF without pulmonary congestion were reproducibly obstructed at follow-up in the current study. There was no indication of asthma in the patient who was not reproducibly obstructed at follow-up.

Our results support previous findings that COPD frequently coexists with HF,[15-17, 20-22] but are in contrast to the study of Brenner et al.[14] who found only 9% of patients with systolic HF to have concomitant COPD, probably explained by the high number of never smokers (45.6%) included in their study. Several factors might explain the high coexistence of these two diseases, including sharing of environmental (mainly smoking) or genetic risk factors, advanced age, systemic inflammation, and a relationship between a reduction in pulmonary and heart function.[2, 5-7, 29-33] Also,

COPD patients are at an increased risk of co-morbidities such as type 2 diabetes, which in turn are an important risk for cardiovascular disease.[30] Furthermore, factors that increase stress on the cardiovascular system or precipitate arrhythmic events can also explain the association between COPD and cardiovascular disease, including hypoxemia, hyperinflation, hyperventilation, neurohumoral disturbances, increased work of breathing and oxygen consumption, pulmonary hypertension, and the use of pulmonary medication.[29, 30, 32, 34] Finally, other factors, such as oxidative stress, endothelial dysfunction, arterial stiffness, and connective tissue degradation have also been suggested to play a role.[32, 34]

Since spirometry is still underutilized even in a tertiary-care facility,[19] it seems reasonable to consider routine spirometry testing in patients with CHF to diagnose or rule out COPD, a co-morbidity with important therapeutic and prognostic implications[2, 10-16, 22] which is still greatly under- and overdiagnosed as found in this study (19% and 32%, respectively). Indeed, diagnostic difficulties have been stressed before, including the overlap in signs, symptoms, and risk factors, the underuse of spirometry despite the fact that objective evidence of airway obstruction is mandatory for diagnosing COPD, and difficulties with interpreting spirometry results, especially in patients with decompensated HF.[2, 4-7, 14] This raises concerns regarding possible inappropriate treatment of COPD in an already vulnerable group of patients and as a result possible adverse impact on health and outcome.

Unfortunately, the current study was not large enough to find predictors of newly diagnosed COPD to make specific recommendations regarding which subgroup of patients should be tested. Also, it should be noted that a large proportion (69,2%) of newly diagnosed COPD patients had only mild airway obstruction that may represent a physiological decline of lung function with age instead of a disease.[35, 36] It is unknown whether an additional diagnosis and treatment of COPD in these patients would improve health outcomes and change their prognosis. This warrants further research to establish the effectiveness of screening of patients with CHF for COPD in terms of symptomatic relief and improvement of the outcome as well as cost-effectiveness of such a policy. Until then, spirometry could be used in CHF patients with pulmonary symptoms despite an adequate treatment for their HF, especially in the presence of risk factors for COPD, such as a smoking history of ≥ 10 PY and occupational exposures. Importantly, spirometry should be used when clinically euvolemic to avoid both misdiagnosis and inappropriate treatment of COPD.[2]

The current study has some limitations that deserve further discussion. It is important to realize that the results may not be applicable to all patients with CHF, since we did not include patients with preserved systolic function. The diagnosis of HF with

preserved systolic function is challenging and particularly difficult to establish in patients with COPD.[5] Thus, to avoid possible overestimation of COPD prevalence in our population, we only included patients with LVSD. Also, patients with more severe HF could have been under-represented in this study because of inability to participate. COPD prevalence may therefore have been somewhat underestimated. Likewise, there may be a recruitment bias in the cohort, given the refusal of 311 patients to provide informed consent. Finally, another limitation is the relatively small number of patients, particularly with COPD. However, included patient numbers are comparable to other recently published studies.[16, 20-22]

Despite these limitations, our findings have potential clinical implications. Our results indicate that confirmatory spirometry does not change a newly established diagnosis of COPD in the vast majority of patients with CHF, provided that PFTs are obtained during stable and non-congested conditions. The results also highlight the need for extensive use of spirometry to decrease the burden of undiagnosed or overdiagnosed COPD in patients with CHF. Evidently, the frequent underdiagnosis and overdiagnosis of COPD is not only a concern in the general population, but also in patients who are regularly monitored in outpatient cardiology clinics. Physicians should bear in mind that both diseases often coexist with important diagnostic and therapeutic difficulties and prognostic implications. Thus, both conditions must be simultaneously assessed and collaboration between cardiologists and pulmonologists is essential.

Conclusions

In conclusion, COPD is a frequent co-morbidity in patients with stable CHF without pulmonary congestion, but is often unrecognized or overdiagnosed. To avoid this and thus ensure adequate treatment of COPD in CHF, PFTs should be routinely obtained in a stable and non-congested condition. Under these conditions a confirmatory spirometry is unnecessary, as it does not change a newly established diagnosis of COPD in the vast majority of patients with CHF.

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CHAPTER 3

COPD in chronic heart failure: less common than previously thought?

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Abstract

Background: Using the fixed ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) < 0.70 instead of the lower limit of normal (LLN) to define chronic obstructive pulmonary disease (COPD) may lead to overdiagnosis of COPD in elderly patients with heart failure (HF) and consequently unnecessary treatment with possible adverse health effects.

Objective: The aim of this study was to determine COPD prevalence in patients with chronic HF according to two definitions of airflow obstruction.

Methods: Spirometry was performed in 187 outpatients with stable chronic HF without pulmonary congestion who had a left ventricular ejection fraction $< 40\%$ (mean age 69 ± 10 years, 78% men). COPD diagnosis was confirmed three months after standard treatment with tiotropium in newly diagnosed COPD patients.

Results: COPD prevalence varied substantially between 19.8% (LLN-COPD) and 32.1% (GOLD-COPD). Twenty-three of 60 patients (38.3%) with GOLD-COPD were potentially misclassified as having COPD (FEV_1/FVC < 0.7 but $>$ LLN). In contrast to patients with LLN-COPD, potentially misclassified patients did not differ significantly from those without COPD regarding respiratory symptoms and risk factors for COPD.

Conclusions: One fifth, rather than one third, of the patients with chronic HF had concomitant COPD using the LLN instead of the fixed ratio. LLN may identify clinically more important COPD than the fixed ratio of 0.7.

Keywords: Chronic heart failure; chronic obstructive pulmonary disease; prevalence; fixed ratio; lower limit of normal.

Introduction

Chronic obstructive pulmonary disease (COPD) frequently coexists with heart failure (HF), leading to poor prognosis as well as diagnostic and therapeutic challenges.[1] However, estimates of COPD prevalence in patients with HF with reduced or preserved left ventricular ejection fraction (LVEF) vary substantially between 9% and 52%, depending on study design, population (age, gender, smoking habits, inpatients versus outpatients, acute versus chronic HF, primary, secondary, or tertiary care), and diagnostic criteria.[1] Although spirometry is considered to be the gold standard for the diagnosis of COPD,[2] data on the prevalence of COPD based on spirometry in patients with HF are scarce.[3-7] Moreover, even when spirometry is used, in general there is still no consensus on how to define COPD.[8-11] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of the fixed ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) < 0.70 for the sake of simplicity.[2] However, a growing body of literature indicates that considering the physiological decline of the FEV_1/FVC ratio with age the use of the fixed ratio may lead to overdiagnosis of COPD in elderly subjects[12-19] and underdiagnosis of COPD in young adults.[15-17, 20] Therefore, to avoid misclassification, the American Thoracic Society/European Respiratory Society (ATS/ERS) recommends the use of statistically derived lower limit of normal (LLN) values for FEV_1/VC that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal.[21] This is particularly important in patients with HF, given that HF is most prevalent among elderly individuals.[22] Thus, COPD prevalence of 30-44% may have been overestimated in prior studies that used the fixed ratio of 0.7 to define COPD in patients with HF.[3-7] Subsequently, an incorrect diagnosis of COPD may result in unnecessary treatment for COPD and undertreatment with beta-blockers, with possible adverse health effects.[8, 23, 24]

Although population-based studies have shown that the application of different criteria to define airflow obstruction dramatically changes the prevalence of COPD,[18, 25-30] it is less well understood to what extent this occurs in patients with chronic HF.[6, 7] Therefore, the primary aim of this study was to determine COPD prevalence according to two definitions of airflow obstruction ($FEV_1/FVC < 0.70$ versus $FEV_1/FVC <$ LLN) in outpatients with stable chronic HF with left ventricular systolic dysfunction (LVSD). The secondary aim of this study was to determine whether patients potentially misclassified as having COPD ($FEV_1/FVC < 0.7$ but $>$ LLN) had clinical features of COPD or those of the healthy population.

Methods

Study design and participants

All patients visiting two outpatient cardiology departments of a large general hospital in The Netherlands were screened for inclusion in this prospective observational study between October 2009 and December 2010. In addition, existing patient lists were used to ensure that the majority of the HF population had been examined for eligibility. Inclusion criteria were stable chronic HF with LVSD, i.e., LVEF $<$ 40%, without pulmonary congestion, New York Heart Association (NYHA) class I-IV, and age $\geq$ 18 years. Chronic HF was defined according to the European Society of Cardiology guidelines.[22] Echocardiography was performed in patients without a recent ($\leq$ 6 months) echocardiography to confirm persisting LVSD. Patients were classified as having stable HF in the absence of hospitalization due to progression of HF within 3 months, change in diuretics within 1 month, 3% or more weight gain within 3 days, and more than 50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) within 1 month when the baseline NT-pro-BNP was 100 pmol/L or higher or more than 100 pmol/L increase of NT-pro-BNP within 1 month when baseline NT-pro-BNP was below 100 pmol/L.[31] Pulmonary congestion was evaluated on standard posterior-anterior and lateral chest radiographs for the presence or absence of alveolar edema, pleural effusion, Kerley-B lines, and/or the redistribution of pulmonary blood flow by independent radiologists who qualitatively assessed the chest radiographs with an overall clinical impression. Patients who were not able to cooperate or undergo spirometry or who had asthma according to their medical chart were excluded. Other exclusion criteria were malignancy with a poor prognosis (survival $<$ 6 months) and participation in another study. Patients who had been hospitalized in the pulmonary department in the past six weeks were included six weeks after discharge to ensure that their pulmonary function was stable at the time of spirometry testing.

In conformity with the ethical guidelines of the 1975 Declaration of Helsinki, this study was conducted with the approval of the regional Research Ethics Committee Arnhem-Nijmegen in The Netherlands (2009/101, NL27798.091.09, ClinicalTrials.gov Identifier NCT01429376). All patients gave written informed consent.

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP according to standard methods used in the hospital laboratory. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including height and weight measurement, spirometry, and a chest radiograph. In addition, a second blood sample (NT-pro-BNP) was taken to determine the stability of HF. A 10-point Borg score[32] was used to evaluate dyspnea at rest.

Additional data were collected from medical records and personal interviews. Arterial blood gas analysis was performed on patients with severe airflow obstruction to determine whether they had chronic respiratory failure.[2]

Patients with newly diagnosed COPD according to either definition were followed up three months after standard treatment for COPD with once-daily 18 μg tiotropium. A third blood sample (NT-pro-BNP) was taken, and spirometry was repeated to confirm persistent airflow obstruction characteristic of COPD in an attempt to exclude asthma as much as possible. Thus only patients with persistent airflow obstruction on three months of follow-up were classified as having COPD.

Spirometry testing

Spirometry (MasterLab Pro; Jaeger; Würzburg, Germany) was performed by trained and certified operators using standard techniques and according to ERS standards for acceptability and reproducibility.[33] The reference values of the European Community for Coal and Steel were used.[33] Subjects with airflow obstruction according to either definition underwent post-bronchodilator spirometry 30 minutes after inhalation of four doses of 100 μg aerosolized salbutamol and four doses of 20 μg aerosolized ipratropium via Volumatic spacer. Participants were instructed not to take broncho-dilators 6-24 hours before the tests, depending on the type of bronchodilator used. At follow-up, salbutamol and ipratropium were used, as previously described, when patients discontinued the use of tiotropium > 24 hours prior to spirometry. Care was taken to match the timing of the second spirometry testing to the first to reduce variations that may occur over a 24-hour period.

Definitions

COPD was defined according to two criteria: post-bronchodilator $FEV_1/FVC < 0.7$ (GOLD-COPD)[2] and post-bronchodilator $FEV_1/FVC <$ LLN (LLN-COPD).[21] *LLN* was regarded as the lower fifth percentile of the frequency distribution of a healthy reference population and was calculated by subtracting 1.64 times the residual standard deviation from the predicted value. The investigator who identified the GOLD or LLN criteria was not blinded to the other rating.

Smoking status was defined as never (< 100 cigarettes in a lifetime), former (≥ 3 months ago), or current smoker (< 3 months). *Smoking pack-years (PY)* were based only on the tobacco cigarette history, and one PY was defined as smoking 20 cigarettes a day for 1 year.

Dyspnea was defined as resting dyspnea or dyspnea at any level of exertion, *chronic cough* as cough ≥ 3 months prior to the study, *chronic sputum production* as the

regular production of sputum for ≥ 3 months in 2 consecutive years, and *aspecific bronchial hyperreactivity (ABHR)* as respiratory symptoms in response to perfumes, the scent of baking or paint, fog, cold air, or temperature changes.

Variables and measures

GOLD-COPD severity staging was determined on the basis of FEV_1 percent predicted according to GOLD criteria: $FEV_1 \geq 80\%$ predicted (stage I, mild), $50\% \leq FEV_1 < 80\%$ predicted (stage II, moderate), $30\% \leq FEV_1 < 50\%$ predicted (stage III, severe), and $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure (stage IV, very severe).[2] *LLN-COPD severity staging* was determined on the basis of FEV_1 percent predicted according to ATS/ERS criteria: $FEV_1 \geq 70\%$ predicted (mild), FEV_1 60-69% predicted (moderate), FEV_1 50-59% predicted (moderately severe), FEV_1 35-49% predicted (severe), and $FEV_1 < 35\%$ predicted (very severe).

Statistical analysis

Descriptive data are presented as the mean ± SD or as a number (%). Baseline characteristics of patients with and without GOLD-COPD were compared using an independent t-test or a Mann-Whitney U test for continuous variables and a chi-square or Fisher's exact test for categorical variables, as appropriate. Differences in continuous variables between three groups of patients (patients with LLN-COPD, patients with potentially misclassified COPD ($FEV_1/FVC < 0.7$ but > LLN), and patients without COPD) were examined with independent analysis of variance. Post hoc analyses were performed using Fisher's LSD test, and a Games-Howell test was used when the assumption of homogeneity of variance was not met. Log transformation was applied to achieve normal distribution when the assumption of normal distribution was not met. Differences in categorical variables between the aforementioned three groups of patients were analyzed with a chi-square test, and the Bonferroni correction was used to control for type I errors. Statistical analyses were performed using the Statistical Package for Social Science version 15.0. All statistical tests were two-sided, and a p-value < 0.05 was considered significant.

Results

Patient characteristics

A cohort of 337 patients with chronic HF was initially included in this study. Thirty-eight patients withdrew informed consent, and 65 patients were excluded for several reasons, as specified in Fig. 1. The remaining 234 patients were included in the study, of whom 187 had stable chronic HF without signs of congestion on chest radiograph. Table 1 shows the characteristics of these patients. The mean age was 69 ± 10 years,

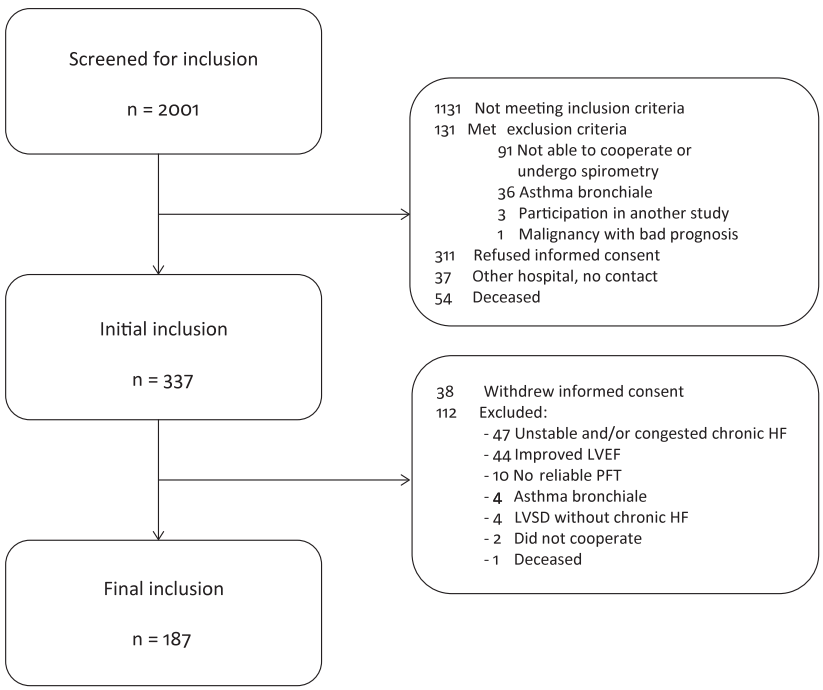

Figure 1 Flow-diagram of screening and final inclusion of study participants. Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; PFT, pulmonary function tests.

the mean was LVEF 29 ± 7%, and 78% of participants were male. The majority of patients had NYHA class II (72%). Almost 60% had an ischemic etiology of HF. Other causes of HF were idiopathic causes (24%), hypertension (6%), valve disease (6%), tachycardiomyopathy (3%), and other causes (2%). Most patients were former or current smokers (83%) and reported symptoms of dyspnea (82%) (Table 2). Other respiratory symptoms were less common.

COPD prevalence

COPD prevalence varied substantially according to the definition used, from 19.8% (LLN-COPD) to 32.1% (GOLD-COPD), after three months of follow-up (Fig. 2A). GOLD-COPD prevalence tended to be higher in men than women (35.6% versus 19.5%, $p = 0.051$). The prevalence of LLN-COPD was not significantly different between men and women (21.9% versus 12.2%, $p = 0.167$). The lack of statistical significance when comparing COPD prevalence according to gender is likely a function of sample

Table 1 Characteristics of patients.

Characteristics	All (n = 187)
Age, years	69 ± 10
Male sex, n (%)	146 (78)
BMI, kg/m^2	28 ± 5
LVEF, %	29 ± 7
NYHA I-II, %	164 (88)
NYHA III-IV, %	23 (12)
Ischemic etiology	110 (59)
Co-morbidity, n (%)	
Myocardial infarction	109 (58)
PCI/CABG	76 (41)
CRT/ICD	64 (34)
Atrial fibrillation	54 (29)
Hypertension	80 (43)
Diabetes mellitus	46 (25)
Medication, n (%)	
ACE-I/ARB	174 (93)
β-blockers	172 (92)
Diuretics	159 (85)
Aldosterone-antagonists	65 (35)
Laboratory data	
NT-pro-BNP1, pmol/L	201 ± 289
NT-pro-BNP2, pmol/L	198 ± 308

Data are presented as the mean ± SD and number (%). Laboratory data 1 and 2 refer to the first (at baseline) and second (one month later) blood samples, respectively. Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B natriuretic peptide; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting.

size. Regardless of the definition used, the prevalence of COPD was higher in current and former smokers than in non-smokers (GOLD-COPD: 43.5%, 35.6%, and 9.4%, respectively, overall $p = 0.008$; LLN-COPD: 26.1%, 23.5%, and 0%, respectively, overall $p = 0.008$), with no significant differences between current and former smokers (Fig. 2A). Interestingly, none of the non-smokers had COPD according to the LLN, while 3 of 32 (9.4%) non-smokers were diagnosed with COPD using the fixed

Table 2 Comparison of GOLD-COPD, LLN-COPD, and potentially misclassified COPD patients with patients without COPD.

	All (n = 187)	GOLD-COPD (n = 60)	LLN-COPD (n = 37)	Potentially misclassified: < 0.7 but > LLN (n = 23)	No COPD (n = 127)
Age, years	69 ± 10	70 ± 9	70 ± 9	71 ± 9	68 ± 11
Male sex, n (%)	146 (78)	52 (87)	32 (86)	20 (87)	94 (74)
Smoking history, n (%)					
Non-smoker	32 (17)	3 (5)*	0 (0)*	3 (13)	29 (23)
Current/former smoker	155 (83)	57 (95)*	37 (100)*	20 (87)	98 (77)
PY, years	24 ± 24	30 ± 28*	33 ± 27*	24 ± 29	21 ± 21
Symptoms, n (%)					
Cough	67 (36)	29 (48)*	19 (51)*	10 (43)	38 (30)
Sputum	43 (23)	17 (28)	13 (35)	4 (17)	26 (20)
Dyspnea	153 (82)	52 (87)	32 (86)	20 (87)	101 (80)
ABHR	55 (29)	26 (43)*	21 (57)*†	5 (22)	29 (23)
Borg dyspnea scale	0.9 ± 1.2	1.1 ± 1.3*	1.5 ± 1.4*†	0.6 ± 1.0	0.8 ± 1.2
Respiratory symptoms or pneumonia in childhood	19 (10)	7 (12)	6 (16)	1 (4)	12 (9)
Family history of asthma or COPD	48 (26)	19 (32)	16 (43)*†	3 (13)	29 (23)
Spirometry					
FEV_1, L	2.5 ± 0.8	2.1 ± 0.7*	1.9 ± 0.7*†	2.4 ± 0.6	2.7 ± 0.8
FEV_1, % predicted	88 ± 21	72 ± 22*	64 ± 18*†	85 ± 22	96 ± 15
FVC, L	3.7 ± 1.0	3.8 ± 1.0	3.8 ± 1.0	3.8 ± 1.0	3.7 ± 1.0
FVC, % predicted	102 ± 19	101 ± 23	100 ± 24	102 ± 24	102 ± 17
FEV_1/FVC, %	68 ± 11	55 ± 10*	49 ± 8*†	64 ± 3*	74 ± 5

Data are presented as the mean ± SD and number (%). Only pre-bronchodilator lung function test results are presented to facilitate the comparison between groups. Abbreviations: ABHR, aspecific bronchial hyperreactivity; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; PY, pack-years. * p-value < 0.05 compared with patients without COPD. † p-value < 0.05, LLN-COPD compared with potentially misclassified COPD patients.

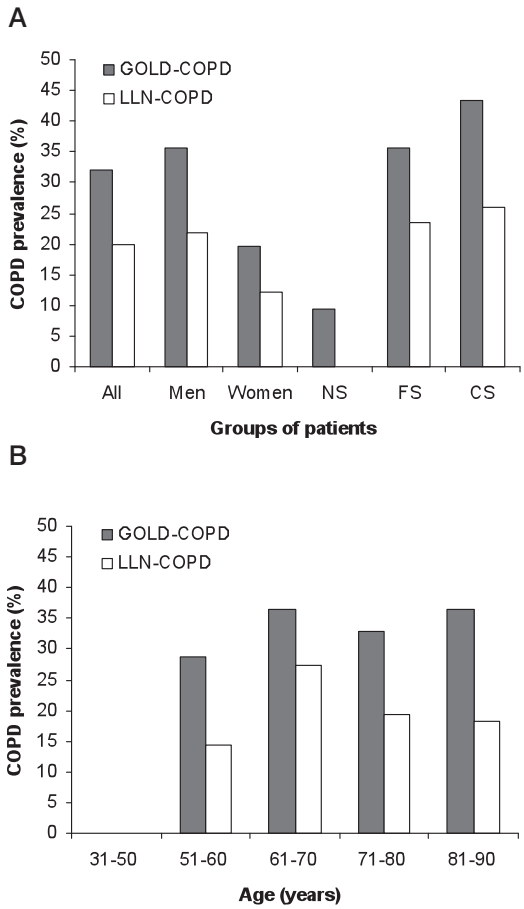

Figure 2 COPD prevalence as defined by two spirometric criteria and according to (**A**) gender and smoking status, and (**B**) age categories. Abbreviations: COPD, chronic obstructive pulmonary disease; CS, current smokers; FS, former smokers; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; NS, non-smokers.

ratio. None of the 9 patients aged between 31 and 50 years were diagnosed with COPD using either definition. COPD prevalence according to other age categories is shown in Fig. 2B. Most patients had mild to moderately severe COPD, while only a minority had severe or very severe COPD (Table 3).

Table 3 Distribution of COPD patients according to GOLD and ATS/ERS severity stages.

Severity class	GOLD-COPD (n = 60)			LLN-COPD
	All (n = 60)	Potentially misclassified: < 0.7 but > LLN (n = 23)	True COPD: < 0.7 and < LLN (n = 37)	(n = 37)
Mild, n (%)	28 (47)	14 (61)	14 (38)	21 (57)
Moderate, n (%)	24 (40)	7 (30)	17 (46)	7 (19)
Moderately severe, n (%)	-	-	-	4 (11)
Severe, n (%)	5 (8)	2 (9)	3 (8)	3 (8)
Very severe, n (%)	3 (5)	0 (0)	3 (8)	2 (5)

Data are presented as number (%). Abbreviations: ATS/ERS, American Thoracic Society/European Respiratory Society. Other abbreviations are identical to those in the Table 2 legend.

Twenty-three of 60 patients (38.3%) with GOLD-COPD were potentially misclassified as having COPD. The majority of these patients had only mild COPD (GOLD stage I: 61% versus 38%, $p = 0.082$) in contrast to patients with true COPD ($FEV_1/FVC < 0.7$ and < LLN) who had more severe disease. These potentially misclassified patients did not differ significantly from patients without COPD, except for a lower ratio of FEV_1/FVC (64 ± 3% versus 74 ± 5%, $p < 0.001$) (Table 2). On the other hand, patients with LLN-COPD did in fact show significant differences compared with patients without COPD: they smoked more (33 ± 27 PY versus 21 ± 21 PY, $p < 0.001$; current/former smokers 100% versus 77%, $p = 0.001$); they had more symptoms of cough (51% versus 30%, $p = 0.016$), Borg dyspnea (1.5 ± 1.4 versus 0.8 ± 1.2, $p = 0.026$) and ABHR (57% versus 23%, $p < 0.001$); they reported a family history of asthma or COPD more often (43% versus 23%, $p = 0.014$); and they had a lower FEV_1 (64 ± 18% predicted versus 96 ± 15% predicted, $p < 0.001$) and FEV_1/FVC ratio (49 ± 8% versus 74 ± 5%, $p < 0.001$) (Table 2). Moreover, LLN-COPD patients also differed significantly from potentially misclassified patients: they had more symptoms of Borg dyspnea (1.5 ± 1.4 versus 0.6 ± 1.0, $p = 0.019$) and ABHR (57% versus 22%, $p = 0.008$); more frequently, they had a family history of asthma or COPD (43% versus 13%, $p = 0.014$); they had a lower FEV_1 (64 ± 18% predicted versus 85 ± 22% predicted, $p = 0.010$) and FEV_1/FVC ratio (49 ± 8% versus 64 ± 3%, $p = 0.002$); and they tended to be more likely current/former smokers (100% versus 87%, $p = 0.052$).

Patients with GOLD-COPD differed significantly from patients without COPD on corresponding variables as those with LLN-COPD, except for one variable; in contrast to patients with LLN-COPD who had a family history of asthma or COPD significantly more often than those without COPD, this was not true for patients with GOLD-COPD (Table 2).

Thirty-four of 60 patients (56.7%) with GOLD-COPD had previously been diagnosed with obstructive lung disease, compared with 25 of 37 patients (67.6%) with LLN-COPD. On the other hand, 16 of 50 (32.0%) patients with a history of obstructive lung disease did not have GOLD-COPD according to their spirometry. The corresponding figure was 25/50 (50.0%) for LLN-COPD.

Discussion

This is one of the few studies to determine the prevalence of COPD in patients with chronic HF using two definitions of COPD, namely, the fixed ratio of 0.7 and the LLN.[6, 7] Our results support previous findings that COPD frequently coexists with chronic HF.[3-7] However, the exact definition of airflow obstruction alters COPD prevalence substantially; one fifth, rather than one third, of the patients with chronic HF had concomitant COPD using the LLN instead of the fixed ratio. LLN may identify clinically more important COPD than the fixed ratio of 0.7 as patients who were potentially misclassified as having COPD, in contrast to patients with LLN-COPD, did not differ significantly from those without COPD in terms of respiratory symptoms and risk factors for COPD.

As expected, using the fixed ratio of 0.7 resulted in a considerably higher prevalence of COPD compared with using the LLN (32.1% versus 19.8%, respectively). This finding is in line with the results of Steinacher et al.[7] who reported COPD prevalence rates of 43.8% according to the GOLD criteria (fixed ratio) and 24.7% according to ATS/ERS criteria (LLN) in 89 outpatients with stable chronic HF. However, this finding was not as well supported in another study of 118 elderly (≥ 65 years) patients with stable chronic HF, most likely because of the selection of patients with ≥ 10 PY (COPD prevalence 30.5% versus 28.8%).[6]

Given the physiological decline of the FEV_1/FVC ratio with age, using the fixed ratio instead of the LLN may result in a diagnosis of COPD in elderly individuals who may not actually have COPD[12-19] which is of particular concern in patients with HF, given that most patients affected by HF are elderly[22] (80.2% of the patients in the current study were older than 60 years). Almost 40% of the patients who were diagnosed with GOLD-COPD based on spirometry were potentially misclassified as having COPD because their FEV_1/FVC ratio was above the LLN.

In clinical practice, decisions are not made on the basis of a single test. Clinical findings, including history and exposure to risk factors, can facilitate the diagnosis of COPD,[2] and the physician ultimately determines the medical significance of an abnormal spirometric value based on these clinical findings. However, these decisions are more complicated in patients with HF due to overlap in signs and symptoms as well as risk factors,[1] which explains, at least in part, the considerable over- and underdiagnosis of COPD observed in this study. The majority (74%) of patients with potentially misclassified COPD had respiratory symptoms (dyspnea, cough, and/or sputum production) combined with a smoking history (current or former smoker), which was also true for patients without COPD, of whom 64% had respiratory symptoms combined with a smoking history. Subsequently, an incorrect diagnosis of COPD and unnecessary treatment as a consequence may be associated with side-effects of pharmacological interventions,[34] especially in elderly patients with HF who usually have several co-morbidities and are prone to polypharmacy. In addition, concerns have been raised regarding the cardiovascular safety profile of bronchodilators. Beta-agonists have been reported to increase the risk for adverse cardiovascular events in patients with obstructive airway disease, with a significant increase in sinus tachycardia and a non-significant trend toward an increase in major cardiovascular events, including ventricular tachycardia, atrial fibrillation, syncope, congestive heart failure, myocardial infarction, cardiac arrest, and sudden death.[35] Moreover, observational studies have shown worse outcomes with bronchodilator use in patients with HF, including increased risk of HF hospitalization, increased mortality rates, in-hospital mechanical ventilation, intravenous vasodilator use, and major cardiovascular events associated with the use of beta-agonists, although further investigation is warranted.[23, 36] Furthermore, inhaled anticholinergics have been reported to be associated with an increased risk of cardiovascular death, myocardial infarction, or stroke among patients with COPD,[37] although recently reassuring cardiovascular safety data have been reported on the long-acting anticholinergic bronchodilator tiotropium (HandiHaler).[38, 39] Nevertheless, bronchodilators, in particular beta-agonists, must be used with caution in patients with underlying cardiac condition such as HF.

Aside from the possible side-effects and adverse cardiovascular events associated with pharmacological treatment for COPD, incorrect diagnosis and interventions for COPD may have a considerable psychological impact on the subject and his/her family and may cause an unnecessary financial burden on society.[8] Furthermore, incorrect diagnosis of COPD may lead to undertreatment with life-saving beta-blockers.[23, 24] Therefore, there is a need for clear diagnostic criteria for COPD to avoid diagnostic confusion, incorrect diagnosis, and inappropriate treatment.

Unfortunately, there is no gold standard for the diagnosis of COPD. The hallmark of the disease is the presence of airflow limitation that is not fully reversible and is usually progressive in nature.[2] However, there is no consensus on the spirometric criteria for the diagnosis of COPD.[8-11] Considering the physiological decline of the FEV_1/FVC ratio with age, the application of statistically derived LLN values for FEV_1/FVC that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal should be preferred to avoid overdiagnosis of COPD in elderly subjects[12-19] and underdiagnosis in young adults.[15-17, 20] However, little is known about the clinical impact of these different criteria and contrasting results have been reported.[12, 20, 40-47] More longitudinal studies are needed to determine which criterion is better and clinically more relevant.[48]

In the current study, patients who were potentially misclassified as having COPD did not differ significantly from those without COPD in terms of respiratory symptoms and risk factors for COPD. On the contrary, patients with LLN-COPD did in fact show significant differences when they were compared with patients without COPD in terms of respiratory symptoms (cough, Borg dyspnea, and ABHR) and risk factors for COPD (smoking history and a family history of asthma or COPD). Moreover, patients with LLN-COPD more frequently had respiratory symptoms (Borg dyspnea and ABHR) and a family history of asthma or COPD compared with patients with potentially misclassified COPD, and they more frequently tended to be current or former smokers. Although this study is not longitudinal in nature, these findings imply that using the LLN may identify clinically more important COPD than the fixed ratio of 0.7. In support of this implication, 67.6% of the patients with LLN-COPD were previously diagnosed with obstructive lung disease, compared to only 39.1% of patients with potentially misclassified COPD.

A limitation of the LLN criterion is its dependence on the prediction equations and on the reference population from which the prediction equations have been drawn. In the USA, ethnically appropriate National Health and Nutrition Examination Survey (NHANES) III reference equations are recommended for those aged 8-80 years.[49] In Europe, the combined reference equations published in the 1993 ERS statement are often used for people aged 18-70 years, with a height range of 155-195 cm in males, and 145-180 cm in females.[33] Recent ATS/ERS guidelines do not recommend any specific set of equations to be used in Europe, but they do suggest the need for a new Europe-wide study to derive updated reference equations.[21] Recently, multi-ethnic spirometric prediction equations for the 3-95 years age range that include appropriate age-dependent lower limits of normal and that can be applied globally have become available.[50]

A limitation to our study is the lack of follow-up to determine how the different spirometric definitions of COPD relate to outcomes such as pulmonary function decline, hospitalization, and mortality. Furthermore, it is important to realize that the prevalence of COPD found in this study may not be applicable to all patients with chronic HF because we did not include patients with preserved systolic function. Additionally, patients with more severe HF could have been under-represented in this study because of their inability to participate.

Clinical implications and implications for future research

Despite these limitations, our findings have potential clinical implications and implications for future research. The results stress the need for a clear definition of COPD, especially in patients with HF in whom the diagnosis of COPD is already complicated due to overlap in signs, symptoms, and risk factors and who are prone to the adverse effects of pharmacological treatment for COPD. Using the LLN results in considerably lower COPD prevalence rates when compared with using the fixed ratio of 0.7: one fifth, rather than one third, of the patients with chronic HF had concomitant COPD. Moreover, LLN may identify clinically more important COPD than the fixed ratio. More longitudinal studies are needed to determine which criterion is better and clinically more relevant in terms of morbidity (symptoms, exercise tolerance, health-related quality of life, exacerbations, hospitalization, pulmonary function decline, use of health recourses, systemic effects such as co-morbidities and systemic biomarkers) and mortality. Finally, future research should focus on the clinical benefit of treating COPD according to either definition in patients with HF and the cardiovascular safety profile of bronchodilators, especially in patients with underlying cardiac condition such as HF.

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CHAPTER 4

Pulmonary function impairment in patients with chronic heart failure: lower limit of normal versus conventional cutoff values

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Abstract

Objective: To determine the prevalence of pulmonary function abnormalities in patients with chronic heart failure (HF) according to recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines using the lower limit of normal (LLN) compared to conventional cutoff values.

Background: Recent ATS/ERS guidelines recommend the use of the LLN instead of the conventional cutoff values to define pulmonary function impairment to avoid misclassification of patients. However, studies addressing the prevalence of pulmonary function abnormalities according to both definitions in patients with chronic HF are lacking.

Results: Diffusion impairment and airway obstruction were found in 44-58% and 26-37% of the patients, respectively, depending on the definition used (LLN versus conventional cutoff values, $p < 0.05$). However, restriction was infrequent, irrespective of the definition used (7% versus 5%, respectively, $p > 0.05$). The LLN identified fewer patients with abnormal lung function, whereas the conventional cutoff values classified more patients with diffusion impairment, airway obstruction, or a mixed category. Twenty-seven percent of patients were misclassified by the conventional cutoff values.

Conclusion: Pulmonary function abnormalities, especially diffusion impairment and airway obstruction, were highly prevalent in patients with chronic HF. Conventional cutoff values classified more patients with diffusion impairment, airway obstruction, or a mixed category compared to the LLN.

Keywords: Chronic heart failure, conventional cutoff values, lower limit of normal, prevalence, pulmonary function impairment.

Introduction

Isolated or combined pulmonary function abnormalities, such as restriction, diffusion impairment, and to a lesser extent airway obstruction are common in patients with chronic heart failure (HF)[1-7] and can contribute to the perception of dyspnea[8] and exercise intolerance.[8-12] Reported prevalence rates vary between 41% and 93% for diffusion impairment,[13-19] between 21% and 55% for restriction,[13-17, 20] and between 14% and 60% for airway obstruction.[13-18, 20, 21] These varying rates across the studies can be partly explained by the usually small number of patients included and differences in study population as well as diagnostic criteria used to define pulmonary function abnormalities. All studies except for one[20] have used conventional cutoff values to define an abnormality. However, the 80% predicted value (i.e. diffusing capacity or total lung capacity < 80% predicted) and the fixed ratio of 0.7 (i.e. forced expiratory volume in 1s to forced vital capacity (FEV_1/FVC) < 0.7) that are traditionally used may misclassify more than 20% of patients leading to false-positive diagnosis in the elderly and underdiagnosis in younger patients.[22] This is explained by the physiological decrease of the FEV_1/FVC ratio with age because the FEV_1 declines more rapidly with age than the FVC in normal subjects.[23] Furthermore, the frequently used 80% predicted value has neither statistical nor physiological validity.[24] To avoid misclassification, recent American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[25] recommend the use of statistically derived lower limit of normal (LLN) values that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal. However, studies using the LLN values to assess the prevalence of pulmonary function abnormalities in patients with HF are lacking. Therefore, the purpose of this study was to determine the prevalence of pulmonary function abnormalities according to recent ATS/ERS guidelines using the LLN in comparison to conventional cutoff values in outpatients with chronic HF.

Methods

Study design and participants

This study was part of a larger prospective cross-sectional study evaluating the prevalence of chronic obstructive pulmonary disease (COPD) in patients with chronic HF (ClinicalTrials.gov Identifier NCT01429376). All patients visiting two outpatient cardiology departments of a large hospital in The Netherlands were screened for inclusion between October 2009 and December 2010. Inclusion criteria were chronic HF[26] with left ventricular systolic dysfunction (LVSD), i.e. left ventricular ejection fraction (LVEF) < 40%, and New York Heart Association class (NYHA) I-IV. Chronic HF was defined according to the European Society of Cardiology guidelines as a clinical

syndrome with symptoms and signs typical of HF and objective evidence of a structural or functional abnormality of the heart at rest.[26] Echocardiography was performed in patients without a recent (≤ 6 months) echocardiography to confirm persisting LVSD. Patients who were not able to cooperate or undergo reliable spirometry according to ERS standards for acceptability and reproducibility[27] or who had a history of asthma were excluded. Other exclusion criteria were malignancy with a poor prognosis (survival < 6 months) and participation in another study. For the current study we also excluded patients with known pulmonary, pleural (with exception of pleural effusion due to HF), neuromuscular, collagen vascular, or other diseases that could affect pulmonary function. Patients with a body mass index (BMI) above 35 were excluded from the restriction prevalence analysis.

Patients were classified as having stable HF in the absence of hospitalization due to progression of HF within 3 months, change in diuretics within 1 month, 3% or more weight gain within 3 days, and more than 50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) within 1 month when the baseline NT-pro-BNP was 100 pmol/L or higher or more than 100 pmol/L increase of NT-pro-BNP within 1 month when baseline NT-pro-BNP was below 100 pmol/L.[28]

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including height and weight measurement, pulmonary function tests (PFTs), a chest radiograph, and a second blood sample (hemoglobin, NT-pro-BNP). Additional data were collected from medical records and personal interviews. Smoking status was defined as never (< 100 cigarettes in a lifetime), former (≥ 3 months ago), or current smoker (< 3 months). Smoking pack-years (PY) were based only on the tobacco cigarette history and one PY was defined as smoking twenty cigarettes a day for one year.

Pulmonary function tests

All participants underwent pre-bronchodilator spirometry (MasterLab Pro, Jaeger, Würzburg, Germany) and measurement of the transfer factor of the lungs for carbon monoxide (TLCO). TLCO was measured with standard single-breath technique and was corrected for the subject's hemoglobin concentration (TLCOc). Body plethysmography was only performed in patients with airway obstruction and/or signs of restriction on spirometry including FVC and/or largest VC < LLN and/or < 80% predicted, since patients with normal spirometry results were not expected to have abnormal findings of body plethysmography. PFTs were performed by trained and certified operators using standard techniques and according to the ERS standards

for acceptability and reproducibility.[27] The European Community for Coal and Steel (ECCS) reference equations were used to calculate predicted values.[27]

Diffusion impairment was defined as TLCOc < LLN (ATS/ERS)[25] and < 80% predicted (conventional cutoff value). Restriction was defined as total lung capacity (TLC) < LLN (ATS/ERS)[25] and < 80% predicted (conventional cutoff value). Airway obstruction was defined as FEV_1/VC < LLN (ATS/ERS)[25] and $FEV_1/FVC < 0.7$ (conventional cutoff value).[29] LLN was regarded as the lower fifth percentile of the frequency distribution of a healthy reference population and it was calculated by subtracting 1.64 times the residual standard deviation from the predicted value based on the ECCS reference equations. Severity of diffusion impairment and airway obstruction using the LLN criteria was categorized according to ATS/ERS guidelines[25] and severity of airway obstruction using the fixed ratio of 0.7 was categorized according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[29]

Chest radiographs

Standard posterior-anterior and lateral chest radiographs were performed and evaluated for the presence or absence of cardiomegaly (cardiothoracic ratio > 0.5), congestion (alveolar edema, pleural effusion, Kerley-B lines, and/or redistribution of pulmonary blood flow) and conditions that belonged to the exclusion criteria. Independent radiologists qualitatively assessed the chest radiographs with an overall clinical impression.

Ethical considerations

The study was approved by the regional Research Ethics Committee Arnhem-Nijmegen in The Netherlands (ClinicalTrials.gov Identifier NCT01429376) and complies with the Declaration of Helsinki. All patients gave written informed consent.

Statistical analysis

Descriptive data are presented as the mean ± SD or as a number (%). Differences in prevalence of pulmonary function abnormalities according to different definitions were analyzed with McNemar's test that compares paired proportions. Differences between groups were analyzed using an independent t-test for continuous variables and a chi-square or Fisher's exact test for categorical variables, as appropriate. Statistical analyses were performed using the Statistical Package for Social Science version 21.0. All statistical tests were two-sided, and a p-value < 0.05 was considered significant.

Results

Patient characteristics

After screening of the entire HF population, a cohort of 164 chronic HF patients was selected for the current study of whom 78% were men (Table 1). The mean age was 68 ± 10 years and the mean LVEF was 28 ± 7%. Seventeen percent were in NYHA class I, 71% in NYHA class II, and 12% in NYHA class III. The majority had stable chronic HF (86%) without signs of congestion on chest radiograph (89%). Other patient characteristics and results of PFTs are presented in Table 1 and Table 2, respectively.

Reliable diffusion measurement could not be obtained in eleven patients due to inability to meet ERS standards for acceptability and reproducibility. These patients were included only in the airway obstruction and restriction prevalence analysis. Similarly, reliable body plethysmography results could not be obtained in three patients. Two of these patients were consequently excluded from the restriction prevalence analysis, because suspected restriction on spirometry could not be confirmed by reliable body plethysmography results. Nine patients had a BMI above 35 and were subsequently excluded from the restriction prevalence analysis.

Pulmonary function impairment

The most noted pulmonary function abnormality was diffusion impairment, which was more prevalent using the conventional cutoff value of 80% instead of the LLN (57.5% versus 44.4%, respectively, $p < 0.05$). The second most prevalent abnormality was airway obstruction, which was more frequent using the fixed ratio of 0.7 instead of the LLN (37.2% versus 25.6%, respectively, $p < 0.05$). In contrast to the high occurrence of diffusion impairment and airway obstruction, restriction was less common, irrespective of the definition used (5.2% versus 7.2%, respectively, $p > 0.05$). This was also true when the two patients with suspected restriction on spirometry but without a reliable body plethysmography result to confirm this were regarded as having restriction (6.5% versus 8.4%, respectively, $p > 0.05$). The frequency of pulmonary function abnormalities according to either definition was not significantly different between current/former smokers and non-smokers. However, patients who had smoked ≥ 10 PY had diffusion impairment and airway obstruction more often compared to those with < 10 PY using the LLN (50.5% versus 34.5% and 31.0% versus 17.2%, respectively, p-value ≤ 0.05). This relationship was lost when using conventional cutoff values (62.1% versus 50.0%, $p = 0.142$, and 40.0% versus 32.8%, $p = 0.353$, respectively).

Table 1 Characteristics of the patients.

Characteristics	n = 164
Age, years	68 ± 10
Male sex, n (%)	128 (78)
BMI, kg/m^2	28 ± 5
LVEF, %	28 ± 7
NYHA class, n (%)	
NYHA I	28 (17)
NYHA II	117 (71)
NYHA III	19 (12)
Stable heart failure, n (%)	141 (86)
Congestion, n (%)	18 (11)
Pleural effusion, n (%)	12 (7)
Cardiomegaly, n (%)	97 (59)
Ischemic etiology	98 (60)
Smoking history, n (%)	
Non-smoker	35 (21)
Current smoker	23 (14)
Former smoker	106 (65)
PY, years	19 ± 20
Dyspnea, n (%)	132 (80)
Co-morbidity, n (%)	
Myocardial infarction	99 (60)
Atrial fibrillation	57 (35)
Hypertension	66 (40)
Diabetes mellitus	40 (24)
PCI/CABG	67 (41)
CRT/ICD	52 (32)
Medication, n (%)	
ACE-I/ARB	153 (93)
β-blockers	149 (91)
Diuretics	135 (82)
Aldosterone-antagonists	63 (38)
Digoxin	20 (12)
Laboratory data	
NT-pro-BNP1, pmol/L	236 ± 316
NT-pro-BNP2, pmol/L	250 ± 375
Hemoglobin, mmol/L	8.6 ± 1.0

Data are presented as the mean ± SD or as a number (%). Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B natriuretic peptide; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; PY, pack-years.

Table 2 Pulmonary function test results.

Pulmonary function tests		
Spirometry, n = 164		
FEV_1, L (% pred.)	2.7 ± 0.8	(93 ± 18)
VC, L (% pred.)	4.0 ± 1.0	(104 ± 17)
FEV_1/VC, %	68 ± 8.0	-
PEF, L/s (% pred.)	8.2 ± 2.3	(108 ± 24)
IC, L (% pred.)	3.0 ± 0.8	(104 ± 21)
FEF_{50}, L/s (% pred.)	2.5 ± 1.1	(62 ± 25)
Diffusing capacity, n = 153		
TLCOc, $mmol.min^{-1}.kPa^{-1}$ (% pred.)	6.7 ± 1.9	(76 ± 16)
TLCOc/VA, $mmol.min^{-1}.kPa^{-1}.L^{-1}$ (% pred.)	1.2 ± 0.3	(90 ± 20)
VA, L (% pred.)	5.7 ± 1.3	(88 ± 13)

Data are presented as the mean ± SD. Pulmonary function data, with exception of FEV_1/VC, are expressed as absolute values and as percent predicted, based on age, height, and sex. Abbreviations: FEF_{50}, forced expiratory flow at 50% of forced vital capacity; FEV_1, forced expiratory volume in 1s; IC, inspiratory capacity; PEF, peak expiratory flow; % pred., percent predicted; VC, largest vital capacity; TLCOc, transfer factor for carbon monoxide corrected for hemoglobin concentration; VA, alveolar volume.

Table 3 shows the prevalence of pulmonary function abnormalities in non-obese (BMI ≤ 35) patients who had complete PFT results (n = 143). More patients had normal pulmonary function using the LLN criteria versus the conventional cutoff values (43% versus 31%). On the other hand, combined diffusion impairment and airway obstruction was more prevalent using the conventional cutoff values compared to the LLN criteria (23% versus 11%). One third of the patients had an isolated diffusion impairment and 10% had isolated airway obstruction. Restriction, either isolated or combined with other abnormalities, was uncommon. Comparable results were noted in a subgroup of stable chronic HF patients without signs of congestion on chest radiograph (n = 113).

Table 4 shows the cross-tabulation of how the patients were classified according to the LLN criteria and the conventional cutoff values. The LLN identified fewer patients with abnormal lung function, whereas the conventional cutoff values classified more patients with diffusion impairment, airway obstruction, or a mixed category. Three patients were classified as obstructive by the FEV_1/VC < LLN criterion and as normal by the FEV_1/FVC < 0.7 criterion. However, all of these patients were obstructive using the FEV_1/VC < 0.7 criterion determined by the largest VC instead of the FEV_1/FVC < 0.7 criterion which contains the VC obtained from a forced expiratory maneuver.

Table 3 Prevalence of pulmonary function abnormalities according to the LLN criteria and the conventional cutoff values in non-obese (BMI ≤ 35) patients with complete pulmonary function test results.

		Total group	Subgroup*
	Definition	n = 143	n = 113
Normal pulmonary function	LLN	61 (43)	49 (43)
	Cutoff value	44 (31)	36 (32)
Isolated diffusion impairment (D)	LLN	41 (29)	36 (32)
	Cutoff value	44 (31)	36 (32)
Isolated restriction (R)	LLN	4 (3)	1 (1)
	Cutoff value	2 (1)	0 (0)
Isolated airway obstruction (O)	LLN	15 (10)	14 (12)
	Cutoff value	15 (10)	13 (12)
D + R	LLN	3 (2)	1 (1)
	Cutoff value	2 (1)	1 (1)
R + O	LLN	1 (1)	1 (1)
	Cutoff value	0 (0)	0 (0)
D + O	LLN	16 (11)	11 (10)
	Cutoff value	33 (23)	27 (24)
R + D + O	LLN	2 (1)	0 (0)
	Cutoff value	3 (2)	0 (0)

Data are presented as number (%). Abbreviations: LLN, lower limit of normal. * Subgroup of patients with stable chronic HF without signs of pulmonary congestion on chest radiograph.

Indeed, the ratio of FEV_1 to VC is capable of accurately identifying more obstructive patterns than its ratio to FVC, because FVC is more dependent on flow and volume histories.[25] A total of 39 (27.3%) patients were classified into discordant cells and were thus misclassified by the conventional cutoff values. Twenty-two of 61 (36.1%) patients with airway obstruction according to the conventional cutoff values were misclassified as having airway obstruction (i.e. < 0.7 but $>$ LLN). Moreover, 20 of 88 (22.7%) patients with diffusion impairment were misclassified as having diffusion impairment (i.e. $< 80\%$ predicted but $>$ LLN). Patients false-positive for airway obstruction were significantly older than patients with or without airway obstruction according to both definitions (74.9 ± 8.3 versus 66.3 ± 12.0 and 66.7 ± 9.7 years, respectively, $p < 0.01$). Patients false-positive for diffusion impairment were significantly older than patients without diffusion impairment according to both definitions (71.8 ± 10.7 versus 66.0 ± 9.0 years, $p = 0.018$), but not significantly older compared to those with true-positive

Table 4 Grouping of patients in different diagnostic categories according to the LLN criteria and the conventional cutoff values.

	Grouping by LLN					
Grouping by cutoff values	Normal	Diffusion impairment	Restriction	Obstruction	Mixed	Total
Normal	40	0	1	3	0	44
Diffusion impairment	10	33	1	0	0	44
Restriction	0	0	2	0	0	2
Obstruction	6	0	0	8	1	15
Mixed	5	8	0	4	21	38
Total	61	41	4	15	22	143

Data are presented as numbers. The concordant cells are shaded gray. Abbreviations: LLN, lower limit of normal.

Table 5 Distribution of patients according to ATS/ERS and GOLD severity stages.

Severity class (ATS/ERS)	**Diffusion impairment (LLN)**	**n (%)**	**Airway obstruction (LLN)**	**n (%)**
Mild	TLCOc > 60% pred.	47 (69)	$FEV_1 \geq 70\%$ pred.	33 (79)
Moderate	TLCOc 40-60% pred.	20 (29)	FEV_1 60-69% pred.	5 (12)
Moderately severe	-	-	FEV_1 50-59% pred.	3 (7)
Severe	TLCOc < 40% pred.	1 (2)	FEV_1 35-49% pred.	1 (2)
Very severe	-	-	$FEV_1 < 35\%$ pred.	0 (0)
Severity class (GOLD)			**Airway obstruction (0.7 fixed ratio)**	**n (%)**
Mild (GOLD I)			$FEV_1 \geq 80\%$ pred.	40 (66)
Moderate (GOLD II)			$50\% \leq FEV_1 < 80\%$ pred.	19 (31)
Severe (GOLD III)			$30\% \leq FEV_1 < 50\%$ pred.	2 (3)
Very severe (GOLD IV)			$FEV_1 < 30\%$ pred.	0 (0)

Data are presented as number (%). Abbreviations: ATS/ERS, American Thoracic Society/European Respiratory Society; FEV_1, forced expiratory volume in 1s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; % pred., percent predicted; TLCOc, transfer factor for carbon monoxide corrected for hemoglobin concentration.

diffusion impairment (71.8 ± 10.7 versus 67.5 ± 11.4 years, p = 0.135). There were no significant differences between these groups regarding the gender.

The majority of patients had mild to moderate severity of diffusion impairment and airway obstruction (Table 5). Only 2 patients with restriction had a TLC between 55% and 64%, whereas the TLC of the remaining patients was between 76% and 83%.

Discussion

The current study defined pulmonary function impairment in patients with chronic HF according to different diagnostic criteria, namely the LLN versus the conventional cutoff values. Our results demonstrate that the LLN identifies fewer HF patients with abnormal lung function, whereas the conventional cutoff values classify more patients as having diffusion impairment, airway obstruction, or a mixed pulmonary impairment. Using the conventional cutoff values instead of the LLN led to misclassification of 27% of the patients. Importantly, the cutoff values failed to identify correctly 34% of patients with normal lung function placing them falsely within a pulmonary dysfunction category. This is explained by the physiological decrease of the FEV_1/FVC ratio with age. The FEV_1 declines more rapidly with age than the FVC in normal subjects.[23] As a result, the fixed ratio of 0.7, that is traditionally used because of its simplicity, may lead to overdiagnosis in the elderly and underdiagnosis in younger patients. Furthermore, the frequently used 80% predicted value has neither statistical nor physiological validity.[24] Limits of normal as the predicted ± 20% can only be accurate when the variance above and below the predicted regression line is proportional with the predicted value (i.e. heteroscedastic: large variance with large values and small variance with small values). However, since this is not the case as the scatter around the predicted regression line is constant (homoscedastic) in pulmonary function measurements, the 80% predicted rule of thumb may lead to false-positive diagnosis in the elderly and shorter individuals with smaller predicted values and underdiagnosis in younger and taller patients with larger predicted values.[22, 24]

Misinterpretation of pulmonary function test results may lead to incorrect diagnosis of disease in elderly patients with HF, such as chronic obstructive pulmonary disease, and as a consequence unnecessary treatment with possible side effects, detrimental psychological impact, and unnecessary financial burden on society. Moreover, results may be interpreted as having more severe or unstable HF due to the effects of HF on pulmonary function and as a result unnecessary intensified treatment for HF. Finally, misdiagnosis may interfere with interpretation of research aimed at understanding the impact of heart failure and several clinical variables on pulmonary

function. For example, patients who had smoked ≥ 10 PY in our study had diffusion impairment and airway obstruction significantly more often compared to those with < 10 PY using the LLN. This relationship was, however, lost when using conventional cutoff values and implies that inclusion of patients who are incorrectly labelled as having pulmonary dysfunction distorted the effect of smoking on pulmonary function by adding noise to our data.

To avoid misclassification, recent ATS/ERS guidelines[25] recommend the use of statistically derived LLN values that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal, thus limiting the chance of false-positive diagnosis to a maximum of 5%. However, studies using the LLN values to assess the prevalence of pulmonary function abnormalities in patients with HF are lacking and pulmonary function abnormalities may have been over-estimated in previous studies that have used conventional cutoff values. Indeed, in this population of mainly old patients with chronic HF significantly higher prevalence rates of diffusion impairment and airway obstruction were noted with the 80% predicted criterion and the fixed ratio of 0.7, respectively, compared to the LLN. Thus, a substantially number of mainly older patients were misclassified as having airway obstruction and diffusion impairment using the conventional cutoff values instead of the LLN.

Even though we used the LLN to better account for age, the occurrence of diffusion impairment and airway obstruction was still high (44% and 26%, respectively). This was also true for patients in a stable clinical condition who did not have signs of pulmonary congestion. Prevalence rates of diffusion impairment and airway obstruction were 41-93%[13-19] and 14-60%,[13-18, 20, 21] respectively, in prior studies that have often included heart transplant recipients. Our results extend these studies by demonstrating that these abnormalities are also highly prevalent in patients with less severe heart failure who were mainly in NYHA class II. However, in contrast to previous reports that have demonstrated high prevalence rates of restriction (21-55%),[13-17, 20] this was quite infrequent in the current study, independent of the definition used. Contrasting results are not explained by the fact that body plethysmography was performed only in patients with an abnormal spirometry result and not in the entire study population, as the chance of missing a restrictive defect is less than 3% when the VC is within the normal range using spirometry. Spirometry is therefore very useful at excluding a restrictive defect.[30] Contrasting results can, however, be attributed to differences in patient characteristics as less severe and mainly stable chronic HF patients without signs of congestion on chest radiograph were enrolled in the current study. In addition, we excluded other diseases that could affect pulmonary function, including obesity. Finally, in contrast to some studies,[16] we have confirmed suspected

restriction on spirometry with body plethysmography, as a reduced VC with normal FEV_1/VC ratio does not prove a restrictive ventilatory defect.[25]

Several factors have been implied to play a role in the etiology of pulmonary function impairment in patients with HF, including the effects of HF itself on pulmonary function in addition to (previously undiagnosed) underlying pulmonary disease and confounding influences such as smoking, coronary artery bypass grafting (CABG), and obesity.[4-7, 31] Irrespective of the causes, pulmonary function abnormalities associated with chronic HF may explain part of the symptoms and functional disability encountered in these patients.[8-12] Moreover, pulmonary function impairment increases with the severity of HF,[9, 11] provides important prognostic information,[32, 33] and may ameliorate or normalize with several treatment modalities, such as pharmacological and non-pharmacological treatment of HF [2, 14, 18, 34-36] and anti-obstructive therapy with bronchodilators.[20, 37-42] Pulmonary function might thus be used as a guide for the evaluation of patients with chronic HF, with respect to severity of disease, prognosis, and response to treatment. More studies involving therapeutic approaches to improve pulmonary function in chronic HF are warranted to determine whether treatment directed at correcting pulmonary function impairment may lead to symptomatic relief, increased exercise capacity, and improvement of the outcome. Furthermore, since little is known about the clinical impact of different criteria of pulmonary dysfunction, longitudinal studies are needed to determine which criterion is clinically more relevant in terms of morbidity (symptoms, exercise tolerance, health-related quality of life, hospitalization, use of health resources) and mortality.

Some limitations of this study deserve further discussion. It is important to realize that these results may not be applicable to all patients with chronic HF, since we did not include patients with preserved systolic function, who seem to have less impaired pulmonary function.[43] The diagnosis of HF with preserved systolic function is challenging and only few patients met our pre-defined criteria of HF with preserved systolic function. Consequently, only patients with LVSD were enrolled in the current study. Furthermore, patients with more severe HF could have been underrepresented in this study because of inability to participate and thus pulmonary function abnormalities might have been underestimated. Finally, since we did not follow the patients prospectively, it remains unknown whether pulmonary function impairment had prognostic implications in our study population and whether this is influenced by different definitions of pulmonary dysfunction. However, pulmonary function did provide significant prognostic information in patients with HF in other studies.[32, 33]

In conclusion, pulmonary function impairment, especially diffusion impairment and airway obstruction, was highly prevalent in patients with chronic HF with LVSD, even

in a stable and non-congested condition and even though we used the LLN to better account for age. The LLN identifies fewer HF patients with abnormal lung function, whereas the conventional cutoff values classify more patients as having diffusion impairment, airway obstruction, or a mixed pulmonary impairment, leading to misclassification of 27% of the patients. In contrast to previous reports, restriction was found to be infrequent in this population of less severe chronic HF, irrespective of the definition used.

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CHAPTER 5

Using the lower limit of normal instead of the conventional cutoff values to define predictors of pulmonary function impairment in subjects with chronic heart failure

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Abstract

Introduction: Using the newer lower limit of normal (LLN) criterion instead of the conventional cutoff values to define pulmonary function abnormalities may result in different predictors of pulmonary function impairment in patients with heart failure (HF). Therefore, we assessed predictors of pulmonary function impairment in subjects with chronic HF according to the LLN in comparison to conventional cutoff values.

Methods: In this prospective cross-sectional study, 164 chronic HF subjects (age 68 $\pm$ 10 years, 78% men, 88% New York Heart Association class I-II) with left ventricular ejection fraction $<$ 40% underwent pulmonary function tests. Predictors of pulmonary function impairment were assessed using the LLN and conventional cutoff values (i.e. 80% predicted value and the fixed ratio of forced expiratory volume in 1s to forced vital capacity $<$ 0.7).

Results: The LLN criterion identified an extra independent predictor of diffusion impairment compared to the 80% predicted value; in addition to body mass index, pack-years (PY), and alveolar volume, female gender also turned out to be an independent predictor. A smoking history of $\geq$ 10 PY was a significant predictor of diffusion impairment and airway obstruction using the LLN criterion, but not using the conventional cutoff values. However, lowering the cutoff points of conventional criteria to match the more stringent LLN and thus avoid overdiagnosis of diffusion impairment and airway obstruction in the elderly, produced similar results as the LLN.

Conclusion: The LLN identifies more predictors of diffusion impairment and airway obstruction compared to conventional cutoff values in subjects with chronic HF with left ventricular systolic dysfunction. However, lowering the conventional cutoff points yielded similar results as the LLN.

Keywords: Chronic heart failure, conventional cutoff values, lower limit of normal, predictors, pulmonary function impairment.

Trial registration: ClinicalTrials.gov Identifier NCT01429376.

Introduction

Isolated or combined pulmonary function abnormalities, such as restriction, diffusion impairment, and to a lesser extent airway obstruction are common in patients with chronic heart failure (HF)[1-7] and can contribute to the perception of dyspnea[8] and exercise intolerance.[8-12] Several factors have been implied to play a role in the etiology of pulmonary function impairment in patients with HF, including the effects of HF itself on pulmonary function in addition to (previously undiagnosed) underlying pulmonary disease and confounding influences such as smoking, coronary artery bypass grafting (CABG), and obesity.[4-7, 13] However, results are not consistent across the studies. For example, although smoking and a history of CABG was associated with more impaired pulmonary function in the study of Johnson et. al.[13] with also weak associations between left ventricular function and both lung volumes as well as diffusing capacity, none of the described pulmonary function abnormalities were found to be related to either smoking status, use of cardiac drugs, chest radiographic changes, hemodynamic findings, or clinical features, including the duration of HF in the study of Wright et. al.[14] Misdiagnosis of pulmonary function abnormalities may have interfered with the interpretation of prior research aiming to investigate the impact of HF and several clinical variables on pulmonary function in this group of patients. Traditionally, the 80% predicted value and the fixed ratio of forced expiratory volume in 1s to forced vital capacity (FEV_1/FVC) < 0.7 have been used to define pulmonary function abnormalities. However, these conventional cutoff values have neither statistical nor physiological validity[15-17] and may misclassify more than 20% of patients leading to false-positive diagnosis in the elderly and underdiagnosis in younger patients.[18] To avoid misclassification, recent American Thoracic Society/ European Respiratory Society (ATS/ERS) guidelines[16] recommend the use of statistically derived lower limit of normal (LLN) values that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal. However, studies using the LLN to assess predictors of pulmonary function impairment in patients with chronic HF are lacking. Therefore, the purpose of this study was to assess predictors of pulmonary function impairment in subjects with chronic HF according to the LLN in comparison to conventional cutoff values (percent predicted and the fixed ratio of FEV_1/FVC).

Methods

Study design and participants

This study was part of a larger prospective cross-sectional study evaluating the prevalence of chronic obstructive pulmonary disease in subjects with chronic HF. All

patients visiting two outpatient cardiology departments of a large hospital in The Netherlands were screened for inclusion between October 2009 and December 2010. Inclusion criteria were chronic HF[19] with left ventricular systolic dysfunction (LVSD), i.e. left ventricular ejection fraction (LVEF) < 40%, and New York Heart Association class (NYHA) I-IV. Chronic HF was defined according to the European Society of Cardiology guidelines.[19] Echocardiography was performed in subjects without a recent (≤ 6 months) echocardiography to confirm persisting LVSD. Subjects who were not able to cooperate or undergo spirometry or who had a history of asthma were excluded. Other exclusion criteria were malignancy with a poor prognosis (survival < 6 months) and participation in another study. For the current study we also excluded subjects with known pulmonary (including chronic obstructive pulmonary disease (COPD)), pleural (with exception of pleural effusion due to HF), neuromuscular, collagen vascular, or other diseases that could affect pulmonary function. Subjects with a body mass index (BMI) above 35 were excluded from the restriction prevalence analysis.

Subjects were classified as having stable HF in the absence of hospitalization due to progression of HF within 3 months, change in diuretics within 1 month, 3% or more weight gain within 3 days, and more than 50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) within 1 month when the baseline NT-pro-BNP was 100 pmol/L or higher or more than 100 pmol/L increase of NT-pro-BNP within 1 month when baseline NT-pro-BNP was below 100 pmol/L.[20]

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including height and weight measurement, pulmonary function tests (PFTs), a chest radiograph, and a second blood sample (hemoglobin, NT-pro-BNP). Additional data were collected from medical records and personal interviews. Smoking status was defined as never (< 100 cigarettes in a lifetime), former (≥ 3 months ago), or current smoker (< 3 months). Smoking pack-years (PY) were based only on the tobacco cigarette history, and one PY was defined as smoking twenty cigarettes a day for one year. Dyspnea was defined as resting dyspnea or dyspnea at any level of exertion.

Pulmonary function tests

All participants underwent pre-bronchodilator spirometry (MasterLab Pro, Jaeger, Würzburg, Germany) and measurement of the transfer factor of the lungs for carbon monoxide (TLCO). TLCO was measured with standard single-breath technique and was corrected for the subject's hemoglobin concentration (TLCOc). During the

measurement of TLCO the alveolar volume (VA) was also obtained and the TLCOc was corrected for the VA (TLCOc/VA, i.e. transfer coefficient for carbon monoxide). Body plethysmography was performed in subjects with airway obstruction according to either definition to assess the presence of hyperinflation. In addition, it was performed in subjects with signs of restriction on spirometry, i.e. (F)VC < LLN and/or < 80% predicted with normal FEV_1/(F)VC ratio, to confirm suspected restriction by measuring the total lung capacity (TLC). In other cases body plethysmography was omitted since abnormal findings of body plethysmography were not expected with normal spirometry results. PFTs were performed by trained and certified operators using standard techniques and according to the ERS standards for acceptability and reproducibility.[21] The European Community for Coal and Steel reference equations were used to calculate predicted values.[21]

Diffusion impairment was defined as TLCOc < LLN (ATS/ERS)[16] and < 80% predicted (conventional cutoff value). Restriction was defined as TLC < LLN (ATS/ERS)[16] and < 80% predicted (conventional cutoff value). Airway obstruction was defined as FEV_1/VC < LLN (ATS/ERS)[16] and FEV_1/FVC < 0.7 (conventional cutoff value).[22] VC was regarded as the largest vital capacity (either slow, forced, inspiratory or expiratory) and FVC as the forced vital capacity obtained during a forced expiratory maneuver. LLN was regarded as the lower fifth percentile of the frequency distribution of a healthy reference population and it was calculated by subtracting 1.64 times the residual standard deviation (RSD) from the predicted value (Table 1). Hyperinflation was defined as the absolute ratio of residual volume (RV) to TLC > 40%.[23]

Chest radiographs

Standard posterior-anterior and lateral chest radiographs were performed and evaluated for the presence or absence of cardiomegaly (cardiothoracic ratio > 0.5), congestion (alveolar edema, pleural effusion, Kerley-B lines, and/or redistribution of pulmonary blood flow) and conditions that belonged to the exclusion criteria. Independent radiologists qualitatively assessed the chest radiographs with an overall clinical impression.

Statistical analysis

Descriptive data are presented as the mean ± SD or as a number (%). Differences in prevalence of pulmonary function abnormalities according to different definitions were analysed with McNemar's test that compares paired proportions. Differences between groups were analyzed using an independent t-test for continuous variables and a chi-square or Fisher's exact test for categorical variables, as appropriate. Differences in pulmonary function between groups of subjects according to NYHA class were analyzed with an independent analysis of variance. Post hoc analyses

Table 1 Regression equations for calculation of predicted values and lower limit of normal for adult men and women.

Variable	Regression equation	1.64 RSD
FEV_1/FVC, %		
Men	-0.18A + 87.21	11.8
Women	-0.19A + 89.10	10.7
TLC, liters		
Men	7.99H – 7.08	1.15
Women	6.60H – 5.79	0.99
RV/TLC, %		
Men	0.39A + 13.96	9.0
Women	0.34A + 18.96	9.6
TLCO, $mmol.min^{-1}.kPa^{-1}$		
Men	11.11H – 0.066A – 6.03	2.32
Women	8.18H – 0.049A – 2.74	1.92

The lower limit of normal (LLN) is calculated by subtracting 1.64 times the residual standard deviation (RSD, figure in the last column) from the predicted value. A, age; FEV_1, forced expiratory volume in 1s; FVC, forced vital capacity; H, height; RV, residual volume; TLC, total lung capacity; TLCO, transfer factor for carbon monoxide.

were performed using Fisher's least-significant difference (LSD) test when the assumption of homogeneity of variance was met. The LSD pairwise comparison is equivalent to performing multiple t-tests on the data. However, it requires the overall ANOVA to be significant and therefore the Type I error is limited to a maximum of 5%. The Games-Howell test was used when the assumption of homogeneity of variance was not met and it was chosen because of unequal sample sizes. Univariate and multivariate logistic regression analysis was performed to identify independent predictors of diffusion impairment according to different definitions. All variables of interest with a univariate p-value $< .05$ were included in the multivariate analysis. Statistical analyses were performed using the Statistical Package for Social Science version 21.0. All statistical tests were two-sided, and a p-value $< .05$ was considered significant.

Results

Subject characteristics

After screening of the entire HF population, a cohort of 164 chronic HF subjects was selected for the current study of whom 78% were men (Table 2). The mean age was 68 ± 10 years and the mean LVEF was 28 ± 7%. Seventeen percent were in NYHA class I, 71% in NYHA class II, and 12% in NYHA class III. The majority had stable chronic HF (86%) without signs of congestion on chest radiograph (89%). Other subject characteristics and results of PFTs are presented in Table 2 and Table 3, respectively.

Reliable diffusion measurement could not be obtained in eleven subjects. These subjects were included only in the airway obstruction and restriction prevalence analysis. Similarly, reliable body plethysmography results could not be obtained in three subjects. Two of these subjects were consequently excluded from the restriction prevalence analysis, because suspected restriction on spirometry could not be confirmed by reliable body plethysmography results. Nine subjects had a BMI above 35 and were subsequently excluded from the restriction prevalence analysis.

Pulmonary function impairment

Prevalence rates of pulmonary function impairment are shown in Table 4. The most noted pulmonary function abnormality was diffusion impairment, which was more prevalent using the conventional cutoff value of 80% predicted instead of the LLN (58% versus 44%, respectively, p-value $<$ .001). The second most prevalent abnormality was airway obstruction, which was more frequent using the fixed ratio of 0.7 instead of the LLN (37% versus 26%, respectively, p-value $=$ .002). In contrast to the high occurrence of diffusion impairment and airway obstruction, restriction was infrequent, irrespective of the definition used (5% versus 7%, respectively, p-value $=$ .25). This was also true when the two patients with suspected restriction on spirometry but without a reliable body plethysmography result to confirm this were regarded as having restriction (7% versus 8%, respectively, p-value $=$ .25). Hyperinflation was present in 46% of 65 patients with airway obstruction or signs of mixed pulmonary dysfunction on spirometry who performed body plethysmography. The definition used to define airway obstruction did not impact the occurrence of hyperinflation.

The frequency of pulmonary function abnormalities according to either definition was not significantly different between current/former smokers and non-smokers. However, subjects who had smoked ≥ 10 PY had diffusion impairment and airway obstruction more often compared to those with $<$ 10 PY using the LLN (51% versus 35% and 31% versus 17%, respectively, p-value $=$ .05). The significance of this relationship

Table 2 Characteristics of the subjects.

Characteristics	n = 164
Age, years	68 ± 10
Male sex, n (%)	128 (78)
BMI, kg/m^2	28 ± 5
LVEF, %	28 ± 7
NYHA class, n (%)	
NYHA I	28 (17)
NYHA II	117 (71)
NYHA III	19 (12)
Stable heart failure, n (%)	141 (86)
Congestion, n (%)	18 (11)
Pleural effusion, n (%)	12 (7)
Cardiomegaly, n (%)	97 (59)
Ischemic etiology	98 (60)
Smoking history, n (%)	
Non-smoker	35 (21)
Current smoker	23 (14)
Former smoker	106 (65)
PY, years	19 ± 20
Dyspnea, n (%)	132 (80)
Co-morbidity, n (%)	
Myocardial infarction	99 (60)
Atrial fibrillation	57 (35)
Hypertension	66 (40)
Diabetes mellitus	40 (24)
PCI/CABG	67 (41)
CRT/ICD	52 (32)
Medication, n (%)	
ACE-I/ARB	153 (93)
βblockers	149 (91)
Diuretics	135 (82)
Aldosterone-antagonists	63 (38)
Digoxin	20 (12)
Laboratory data	
NT-pro-BNP1, pmol/L	236 ± 316
NT-pro-BNP2, pmol/L	250 ± 375
Hemoglobin, mmol/L	8.6 ± 1.0

Data are presented as the mean ± SD or as a number (%). ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B natriuretic peptide; NYHA, New York Heart Association; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; PY, pack-years.

Table 3 Pulmonary function test results.

Pulmonary function tests		
Spirometry, n = 164		
FEV_1, liters (% pred.)	2.7 ± 0.8	(93 ± 18)
VC, liters (% pred.)	4.0 ± 1.0	(104 ± 17)
FEV_1/VC, %	68 ± 8.0	-
Diffusing capacity, n = 153		
TLCOc, $mmol.min^{-1}.kPa^{-1}$ (% pred.)	6.7 ± 1.9	(76 ± 16)
TLCOc/VA, $mmol.min^{-1}.kPa^{-1}/L$ (% pred.)	1.2 ± 0.3	(90 ± 20)
VA, L (% pred.)	5.7 ± 1.3	(88 ± 13)
Body plethysmography, n = 70*		
TLC, liters (% pred.)	6.7 ± 1.3	(100 ± 16)
RV, liters (% pred.)	2.7 ± 0.6	(107 ± 24)
RV/TLC, % (% pred.)	40 ± 7	(99 ± 18)
ITGV, liters (% pred.)	4.0 ± 0.9	(112 ± 21)
Raw, $kPa.L^{-1}.s$ (% pred.)	0.4 ± 0.2	(121 ± 60)
sGaw, $kPa^{-1}.s^{-1}$ (% pred.)	0.9 ± 0.4	(98 ± 45)

Data are presented as the mean ± SD. Pulmonary function data, with exception of FEV_1/VC, are expressed as absolute values and percent predicted based on age, height, and sex. FEV_1, forced expiratory volume in 1s; ITGV, intra-thoracic gas volume; % pred., percent predicted; sGaw, specific airway conductance; TLC, total lung capacity; TLCOc, transfer factor for carbon monoxide corrected for hemoglobin concentration; Raw, airway resistance; RV, residual volume; VA, alveolar volume; VC, largest vital capacity. * Reasons for performing body plethysmography: airway obstruction (n = 58), signs of restriction (n = 5); signs of mixed pulmonary dysfunction (n = 7).

was lost when using conventional cutoff values (62% versus 50%, p-value = .14, and 40% versus 33%, p-value = .35, respectively). On the other hand, lowering the conventional cutoff value to 75% for diffusion impairment (TLCOc < 75% predicted) and 0.65 for airway obstruction (FEV_1/FVC ratio < 0.65) yielded significant differences in the occurrence of diffusion impairment and airway obstruction when comparing groups of patients who had smoked ≥ 10 PY versus < 10 PY (51% versus 33%, p-value = .03, and 27% versus 9%, p-value = .01, respectively). The frequency of airway obstruction according to either definition was not significantly different between men and women (LLN: 27% versus 19%, respectively, p-value = .34; fixed ratio of 0.7: 41% versus 25%, respectively, p-value = .09). However, although the frequency of diffusion impairment according to the 80% predicted value was not

Table 4 Prevalence of pulmonary function impairment according to smoking status and gender using the LLN versus (adjusted) conventional cutoff values.

	All	NS	FS/CS		PY < 10	PY ≥ 10		Men	Women	
	n = 164	n = 35	n = 129	p-value	n = 64	n = 100	p-value	n = 128	n = 36	p-value
Diffusion impairment*										
LLN	44	41	46	.63	35	51	.05	40	61	.04
Conventional cutoff values	58	53	59	.57	50	62	.14	54	70	.11
Adjusted conventional cutoff values†					33	51	.03	33	58	.01
Airway obstruction										
LLN	26	14	29	.08	17	31	.05	27	19	.34
Conventional cutoff values	37	26	40	.11	33	40	.35	41	25	.09
Adjusted conventional cutoff values†					9	27	.01			
Restriction*										
LLN	7	7	7	1.00	7	7	1.00	9	0	.12
Conventional cutoff values	5	3	6	.70	3	6	.49	7	0	.21

Data are presented as percentages. CS, current smokers; FS, former smokers; LLN, lower limit of normal; NS, non-smokers; PY, pack-years; *Analysis was performed in a total of 153 subjects. †TLCOc < 75% for PY and < 70% for gender differences. FEV_1/FVC ratio < 0.65.

significantly different between men and women (54% versus 70%, respectively, p-value = .11), women had diffusion impairment significantly more often than men using the LLN (61% versus 40%, respectively, p-value = .04). Lowering the conventional cutoff value to 70% (TLCOc < 70% predicted) yielded significant differences between women and men in the occurrence of diffusion impairment (58% versus 33%, p-value = .01).

Subjects with a higher NYHA class had lower FEV_1, TLCOc, and VA (Table 5). Subjects who had smoked ≥ 10 PY had lower FEV_1, FEV_1/VC ratio and TLCOc than those with < 10 PY (Table 6). Subjects with pulmonary congestion, pleural effusion, or cardiomegaly on chest radiograph had lower lung volumes and diffusing capacity than those without pulmonary congestion, pleural effusion, or cardiomegaly (Table 7). TLCOc corrected for VA, however, was comparable between the groups. A history of CABG was associated with lower lung volumes.

Table 5 Pulmonary function test results according to New York Heart Association class.

	Total group	NYHA I	NYHA II	NYHA III	
	n = 164	n = 28	n = 117	n = 19	p-value
FEV_1, % pred.	93 ± 18	98 ± 18†	94 ± 17	84 ± 19	.03
VC, % pred.	104 ± 17	107 ± 16	104 ± 16	97 ± 21	.12
FEV_1/VC, %	68 ± 8.0	68 ± 8	68 ± 8	68 ± 9	.91
TLCOc, % pred.‡	76 ± 16	85 ± 10*†	74 ± 16	73 ± 15	< .001
TLCOc/VA, % pred.‡	90 ± 20	94 ± 15	88 ± 20	92 ± 23	.33
VA, % pred.‡	88 ± 13	94 ± 10*†	88 ± 13	83 ± 15	.03

Data are presented as mean ± SD. Abbreviations as in Table 2 and 3 legends. P-values refer to differences in pulmonary function between groups of subjects according to NYHA class (independent analysis of variance). * p-value < .05, NYHA I versus NYHA II; †p-value < .05, NYHA I versus NYHA III. No significant differences in pulmonary function were found between NYHA class II and III. ‡ Analysis was performed in a total of 153 subjects.

Univariate and multivariate logistic regression analysis

Since the most frequently observed abnormality in pulmonary function was diffusion impairment, we performed a univariate and multivariate logistic regression analysis to identify independent predictors of diffusion impairment according to different definitions (Table 8). All variables of interest with a univariate p-value < .05 were

Table 6 Pulmonary function test results according to smoking status.

	Total group	PY < 10	PY ≥ 10	
	n = 164	n = 64	n = 100	p-value
FEV_1, % pred.	93 ± 18	97 ± 19	91 ± 17	.05
VC, % pred.	104 ± 17	105 ± 19	103 ± 15	.39
FEV_1/VC, %	68 ± 8.0	69 ± 7	67 ± 9	.04
TLCOc, % pred.*	76 ± 16	80 ± 13	74 ± 17	.02
TLCOc/VA, % pred.*	90 ± 20	93 ± 17	88 ± 21	.10
VA, % pred.*	88 ± 13	89 ± 13	88 ± 13	.49

Data are presented as mean ± SD. Abbreviations as in Table 2 and 3 legends. *Analysis was performed in a total of 153 subjects.

included in the multivariate analysis. These included female sex, BMI, PY, NT-pro-BNP, and VA to identify independent predictors of diffusion impairment according to the LLN. In addition, BMI, cardiomegaly, PY, NT-pro-BNP, and VA were included to identify independent predictors of diffusion impairment according to the 80% predicted value. Multivariate analysis showed female gender, BMI, PY (continuous variable), and VA to be independent predictors of diffusion impairment according to the LLN. Similar variables were found to be associated with diffusion impairment according to the 80% predicted value, except for female gender. However, female gender became an independent predictor of diffusion impairment after lowering the conventional cutoff value to 70% (TLCOc < 70% predicted, odds ratio 3.7 [1.6 – 8.7], p-value = .00). PY as a dichotomous variable (< 10 or ≥ 10) was an independent predictor of diffusion impairment according to the LLN (multivariate odds ratio 2.3 [1.1 - 4.9], p-value .03), but not according to the 80% predicted value (univariate odds ratio 1.6 [0.8 - 3.2], p-value .14). However, smoking ≥ 10 PY became an independent predictor of diffusion impairment after lowering the conventional cutoff value to 75% (TLCOc < 75% predicted, multivariate odds ratio 2.7 [1.3 – 5.9], p-value = .01).

A smoking history of ≥ 10 PY was a significant predictor of airway obstruction (univariate logistic analysis) using the LLN criterion (odds ratio 2.2 [1.0 - 4.7], p-value .05), but not using the fixed ratio of 0.7 (odds ratio 1.4 [0.7 - 2.6], p-value .35). However, smoking ≥ 10 PY became a significant predictor of airway obstruction after lowering the fixed ratio of FEV_1/FVC to < 0.65 as cutoff point (odds ratio 3.6 [1.4 – 9.2], p-value = .01). No other predictors of airway obstruction were found using either definition (data not shown) and thus a multivariate logistic regression analysis could not be performed.

Table 7 Pulmonary function test results according to the presence or absence of pulmonary congestion, pleural effusion, cardiomegaly, and a history of coronary artery bypass grafting.

	Total group	Congestion –	Congestion +	Pleural effusion –	Pleural effusion +	Cardiomegaly –	Cardiomegaly +	CABG –	CABG +
	n = 164	n = 146	n = 18	n = 152	n = 12	n = 67	n = 97	n = 128	n = 36
FEV_1, % pred.	93 ± 18	95 ± 18	82 ± 17*	93 ± 18	84 ± 17†	98 ± 16	90 ± 19*	95 ± 17	88 ± 19†
VC, % pred.	104 ± 17	105 ± 17	94 ± 14*	104 ± 17	94 ± 13*	110 ± 14	100 ± 17*	106 ± 16	96 ± 18*
FEV_1/VC, %	68 ± 8.0	68 ± 8	65 ± 8	68 ± 8	66 ± 8	68 ± 9	68 ± 8	68 ± 8	68 ± 9
TLCOc, % pred.‡	76 ± 16	77 ± 15	68 ± 15*	77 ± 15	66 ± 18*	79 ± 16	74 ± 15*	77 ± 16	72 ± 14
TLCOc/VA, %pred.‡	90 ± 20	90 ± 19	89 ± 22	90 ± 19	88 ± 24	86 ± 18	92 ± 21	89 ± 20	92 ± 20
VA, % pred.‡	88 ± 13	89 ± 13	80 ± 10*	89 ± 13	79 ± 11*	95 ± 11	84 ± 12*	90 ± 12	81 ± 14*

Data are presented as mean ± SD. Abbreviations as in Table 2 and 3 legends. *p-value < .05; †p-value .05-.07. ‡Analysis was performed in a total of 153 subjects.

Table 8 Determinants of diffusion impairment according to the LLN criteria and conventional cutoff values.

	Diffusion impairment			
	TLCOc < LLN	TLCOc < LLN	TLCOc < 80% pred.	TLCOc < 80% pred.
	Univariate	Multivariate†	Univariate	Multivariate‡
Age, years	1.001 (0.971 - 1.032)		1.023 (0.992 - 1.055)	
Female sex	2.308 (1.049 – 5.075)*	2.970 (1.257 – 7.019)*	1.946 (0.853 – 4.440)	
BMI, kg/m^2	0.916 (0.847 - 0.990)*	0.898 (0.821 – 0.982)*	0.905 (0.838 – 0.977)*	0.872 (0.796 – 0.956)*
LVEF, %	0.962 (0.920 - 1.006)		0.964 (0.921 – 1.008)	
NYHA class I vs III	0.298 (0.077 – 1.145)		0.424 (0.124 – 1.451)	
NYHA class II vs III	1.273 (0.467 – 3.470)		1.380 (0.504 – 3.781)	
Congestion	2.008 (0.678 - 5.954)		3.263 (0.881 - 12.080)	
Cardiomegaly	1.823 (0.944 - 3.521)		2.374 (1.227 – 4.592)*	
PY, years	1.021 (1.003 - 1.038)*	1.023 (1.004 – 1.043)*	1.002 (1.003 – 1.041)*	1.025 (1.003 – 1.048)*
CABG	1.221 (0.554 - 2.690)		1.724 (0.749 - 3.966)	
NT-pro-BNP, pmol/L	1.001 (1.000 - 1.002)*		1.002 (1.000 – 1.003)*	
VA, % pred.	0.968 (0.943 – 0.994)*	0.965 (0.936 – 0.995)*	0.962 (0.936 – 0.989)*	0.961 (0.928 – 0.994)*
ACE-I	0.944 (0.467 - 1.908)		1.041 (0.513 – 2.111)	
Aldosterone-antagonists	1.800 (0.930 - 3.484)		1.520 (0.778 – 2.972)	

Data are presented as odds ratio's and confidence intervals. LLN, lower limit of normal. Other abbreviations as in Table 2 and 3 legends. *p < .05. †Nagelkerke R_2 = .22. ‡Nagelkerke R_2 = .23.

Discussion

The current study showed that the definition used for pulmonary function impairment impacts the role of gender and smoking on pulmonary function in subjects with chronic HF with LVSD. The LLN criterion identified an extra independent predictor of diffusion impairment compared to the 80% predicted value; in addition to BMI, PY, and VA, female gender also turned out to be an independent predictor. A smoking history of ≥ 10 PY was a significant predictor of diffusion impairment and airway obstruction using the LLN criterion, but not using the conventional cutoff values. However, making the conventional cutoff values more stringent by lowering the cutoff point yielded similar results as the LLN. Lower lung volumes were found in subjects with pulmonary congestion, cardiomegaly, and a history of CABG.

In the current study, the conventional cutoff values classified more patients as having diffusion impairment and airway obstruction compared to the LLN. This is explained by the physiological decrease of the FEV_1/FVC ratio with age. The FEV_1 declines more rapidly with age than the FVC in normal subjects.[24] As a result, the fixed ratio of 0.7, that is traditionally used because of its simplicity, may lead to overdiagnosis in the elderly and underdiagnosis in younger patients.[24] Furthermore, the frequently used 80% predicted value has neither statistical nor physiological validity.[15-17] Limits of normal as the predicted ± 20% can only be accurate when the variance above and below the predicted regression line is proportional with the predicted value (i.e. heteroscedastic: large variance with large values and small variance with small values). However, since this is not the case as the scatter around the predicted regression line is constant (homoscedastic) in pulmonary function measurements, the 80% predicted rule of thumb may lead to false-positive diagnosis in the elderly and shorter individuals with smaller predicted values and underdiagnosis in younger and taller patients with larger predicted values.[15-17]

Misdiagnosis of pulmonary function abnormalities by the conventional cutoff values may have interfered with the interpretation of prior research aiming to investigate the impact of HF and several clinical variables on pulmonary function. This may explain part of the inconsistencies across the studies. In fact, a smoking history of ≥ 10 PY was a significant predictor of diffusion impairment and airway obstruction using the LLN criterion, but not using the conventional cutoff values. This implies that inclusion of subjects who are incorrectly labeled as having pulmonary dysfunction distorted the effect of smoking on pulmonary function. Indeed, lowering the conventional cutoff values to match the more stringent LLN and thus avoid overdiagnosis of diffusion impairment and airway obstruction in the elderly, produced similar results as the LLN. Similarly, female gender was an independent predictor of diffusion impairment

according to the LLN, but not according to the 80% predicted value. However, decreasing the cutoff point to define diffusion impairment showed comparable findings to the LLN. On the other hand, by increasing the LLN to the 10th percentile, the association between female gender and diffusion impairment was lost (data not shown). This is explained by the fact that the lower ranges of diffusing capacity represented relatively more women than men. In summary, the LLN criterion identified more predictors of diffusion impairment and airway obstruction compared to conventional cutoff values in subjects with chronic HF with LVSD. However, when conventional cutoff points were lowered to match the more stringent LLN criterion, the same effects were seen.

The effect of different definitions has also been put forward in the study of de Marco et al.,[25] who have shown that the role of age, sex, former smoking, and low BMI on the development of COPD differs according to the definition used to define COPD. They suggested the need for a definition of COPD that is not exclusively based on spirometry.

Little is known about the clinical impact of different criteria of pulmonary dysfunction. Mannino and Diaz-Guzman[26] followed up the mortality data of a large number of subjects from the NHANES III classified as normal, obstructed, or restricted using conventional cutoff values and the LLN. They found that subjects classified as normal using the LLN but obstructed or restricted using conventional cutoff values had a higher risk of mortality than normal subjects in up to 18 years of follow-up. This finding suggests that conventional criteria may identify at-risk patients who would have been missed using the LLN. This study was limited by the lack of post-bronchodilator pulmonary function test results, other outcome parameters than mortality, and the lack of comparison between subjects with mild airway obstruction according to conventional cutoff values ($FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted) and normal subjects according to the LLN (FEV_1/FVC, FEV_1, and $FVC \geq LLN$). More longitudinal studies are warranted to determine which criterion is clinically more relevant in terms of morbidity (symptoms, exercise tolerance, health-related quality of life, hospitalization, use of health recourses) and mortality. Since we did not follow our subjects prospectively, it remains unknown whether pulmonary function impairment had prognostic implications in our study population and whether this is influenced by different definitions of pulmonary dysfunction.

Several factors have been implied to play a role in the etiology of pulmonary function impairment in patients with HF, including the effects of HF itself on pulmonary function in addition to (previously undiagnosed) underlying pulmonary disease and confounding influences such as smoking, CABG, and obesity.[4-7, 13]

Diffusion impairment has been thought to be related to the thickening of alveolar-capillary membrane due to hydrostatic mechanical injury, interstitial edema, remodeling, and fibrosis.[1, 2, 4-6, 27] Because heart transplantation does not affect or may even worsen pulmonary diffusing capacity despite an improvement in hemodynamic status and lung volumes,[28] it has been suggested that reduced diffusing capacity in CHF may be related to permanent damage to the alveolar-capillary membrane.[2] Other possible causes of diffusion impairment in HF include reduced lung and pulmonary capillary blood volumes, ventilation-perfusion mismatch, recurrent pulmonary emboli, smoking, and cardiopulmonary bypass.[4-6, 13] The results of our study showed a higher NYHA class, smoking of ≥ 10 PY, pulmonary congestion, pleural effusion, and cardiomegaly to be associated with more impaired diffusing capacity, the latter three probably due to their negative effects on lung volume. Indeed, diffusing capacity corrected for VA was not significantly different between the groups. Also, although VA turned out to be an independent predictor of diffusion impairment, pulmonary congestion and cardiomegaly were not. In contrast to previous reports,[29-31] the use of angiotensin-converting enzyme inhibitors and aldosterone-antagonists was not associated with increased diffusing capacity. Also, diffusing capacity was not significantly different between groups of subjects with or without a history of CABG. Independent predictors of diffusion impairment were BMI, PY (continuous variable), and VA, whereas the role of gender and having smoked ≥ 10 PY depended on the definition used to define diffusion impairment. Although the underlying mechanisms are not clear, women seemed to be more sensitive to the detrimental effects of HF on diffusing capacity. Gender differences in pulmonary function have been recognized before, but not specifically in the HF population. Adult women have been reported to have lower resting lung diffusing capacity corrected for hemoglobin, smaller lung volumes, and lower maximal expiratory flow rates, even when corrected for age and standing height relative to men.[32] It has been suggested that these gender differences in part can be explained by pulmonary structural differences (fewer total number of alveoli and smaller airway diameter relative to lung size) and hormonal influences in women.[32] More research is needed regarding the influence of gender on pulmonary function in general and specifically in the HF population. The protective association between a higher BMI and less likelihood of having diffusion impairment has to our knowledge not been described before in subjects with chronic HF. However, some studies in healthy obese non-smokers have suggested that diffusing capacity may be increased in extremely obese subjects, probably as a result of the increase in blood volume.[33]

Restriction has been linked to cardiomegaly, pleural effusion, respiratory muscle weakness, CABG, fibrosis from chronic congestion, and reduced lung compliance due to chronic vascular engorgement, interstitial/alveolar fluid accumulation, and chronic remodeling of the pulmonary vasculature due to elevated left atrial pressure.[1, 4-6, 13, 34, 35]

In line with expectations, we found lung volumes to be lower in subjects with pulmonary congestion, pleural effusion, cardiomegaly, and a history of CABG.

Airway obstruction has been attributed to alveolar fluid accumulation, bronchial mucosal swelling, peribronchial edema and fibrosis, squamous metaplasia of bronchial epithelial cells induces by transforming growth factor-ß from the failing heart, geometric decrease in airway size from reduction in lung volume, abnormalities of autonomic control, neurohumoral bronchoconstriction, bronchial hyperresponsiveness, and smoking,[4-7, 13, 36] although results are not consistent.[14] Our study showed more impaired FEV_1/VC ratio in patients who had smoked ≥ 10 PY. Also, having smoked ≥ 10 PY was a significant predictor of airway obstruction, but this depended on the definition used to define airway obstruction. Although we have excluded patients with known COPD or other obstructive lung disease, we cannot rule out the possibility that some of the patients with airway obstruction had previously undiagnosed COPD, as most patients were current or former smokers. In fact, 16% (LLN) to 24% (conventional cutoff values) of the patients had post-bronchodilator airway obstruction after inhaling 400 mcg salbutamol and 80 mcg ipratropium. These patients had more symptoms of cough and sputum than those without post-bronchodilator airway obstruction (data not shown). Also, patients who were current or former smokers tended to have more often post-bronchodilator airway obstruction than those who had never smoked (LLN: 19% versus 6%, $p = .06$; conventional cutoff values: 27% versus 11%, $p = .05$). However, hyperinflation, which has been found to be a valid indicator of true COPD in patients with congested HF,[37] was not significantly different between groups of patients with persistent airway obstruction after bronchodilation and those with reversible airway obstruction (data not shown). Although airway obstruction in HF has also been attributed to pulmonary congestion, FEV_1/VC ratio was not significantly different between groups of subjects with and without pulmonary congestion in our study. This, however, does not exclude the contribution of pulmonary congestion to small airways obstruction.

Importantly, airway obstruction may lead to hyperinflation of the lungs due to expiratory flow limitation and air trapping, which was found in almost half of our patients with airway obstruction as defined by an increased RV/TLC ratio. This may contribute to symptoms of dyspnea, poor exercise tolerance, increased work of breathing and oxygen consumption, respiratory muscle dysfunction, and adverse impact on cardiac function by decreasing the preload.[38] Thus, irrespective of the causes, pulmonary function abnormalities associated with chronic HF may explain part of the symptoms and functional disability encountered in these patients.[8-12] Moreover, pulmonary function impairment increases with the severity of HF,[9, 11] provides important prognostic information,[39-42] and may ameliorate or normalize with

several treatment modalities, such as pharmacological and non-pharmacological treatment of HF[2, 28, 43-46] and anti-obstructive therapy with bronchodilators.[47-53] Pulmonary function might thus be used as a guide for the evaluation of patients with chronic HF, with respect to severity of disease, prognosis, and response to treatment.

Some limitations of this study deserve further discussion. It is important to realize that these results may not be applicable to all patients with chronic HF, since we did not include subjects with preserved systolic function, who seem to have less impaired pulmonary function.[54] Furthermore, patients with more severe HF could have been underrepresented in this study because of inability to participate and thus pulmonary function abnormalities might have been underestimated. Finally, considering the relatively small number of subjects included in the current study, in particular women and non-smokers, further research is needed to confirm our results.

In conclusion, the LLN identifies gender as an extra independent predictor of diffusion impairment and a smoking history of ≥ 10 PY as an additional predictor of both diffusion impairment and airway obstruction compared to conventional cutoff values in subjects with chronic HF with LVSD. However, when conventional cutoff points were lowered to match the more stringent LLN criterion, the same effects were seen. Our results stress the need for clear definitions of pulmonary function abnormalities. More longitudinal studies are warranted to determine which criterion is clinically more relevant. Specifically, future research should focus on better characterizing the potentially misclassified group of patients who are above the LLN but below the conventional cutoff values. Do these patients have worse outcome with higher morbidity and mortality rates that is amenable to treatment or do they present clinical features similar to those with CHF but without pulmonary dysfunction? Finally, more research is needed regarding the influence of gender on pulmonary function in the HF population and the possible underlying pathophysiologic mechanisms.

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CHAPTER 6

Bronchodilator responsiveness in patients with chronic heart failure

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Abstract

Objective: The aim of this study was to evaluate the effect of inhaled bronchodilators on pulmonary function and dyspnea in patients with chronic heart failure (HF).

Background: Conflicting data exist on whether bronchodilators may improve pulmonary function and dyspnea in patients with chronic HF.

Methods: In this retrospective observational study we analyzed data of 116 chronic HF outpatients with systolic dysfunction who underwent spirometry and Borg dyspnea measurements before and after inhalation of 400 μg salbutamol and 80 μg ipratropium. Patients with chronic obstructive pulmonary disease (COPD) or asthma were excluded.

Results: Bronchodilators fully reversed airway obstruction (AO) in 25 of 64 (39.1%) patients with pre-bronchodilator AO. All spirometric measurements, except for forced vital and inspiratory capacities, improved significantly post-bronchodilation. Absolute and percent improvements in forced expiratory volume in 1 s (FEV_1) were more pronounced in patients with persistent AO post-bronchodilation compared to those without AO (0.19 $\pm$ 0.18L and 8.4 $\pm$ 7.3% versus 0.11 $\pm$ 0.12L and 4.3 $\pm$ 4.0%, $p < 0.05$). Significant bronchodilator responsiveness of FEV_1 (> 200 mL and > 12%) was noted in 12.1% and was more frequent in patients with persistent AO and fully reversible AO than in those without AO (23.1% and 16.0% versus 1.9%, $p < 0.05$). We measured a small, albeit significant improvement in dyspnea (0.7 $\pm$ 1.2 versus 0.9 $\pm$ 1.3, $p = 0.002$).

Conclusions: Inhaled bronchodilators may have an additional role in the management of patients with chronic HF because of their potential to improve pulmonary function, especially in those with AO. The clinical usefulness and possible adverse events of bronchodilators need to be further established.

Keywords: Chronic heart failure; bronchodilator responsiveness; salbutamol; ipratropium; airway obstruction.

Introduction

Pulmonary function abnormalities, such as diffusion impairment, restriction, and airway obstruction (AO), are common in patients with heart failure (HF)[1, 2] and may contribute to the perception of dyspnea and exercise intolerance.[3] Treatment directed at reversing AO with bronchodilators may have an additional role in the management of these patients. There are, however, only few studies concerning the beneficial effects of bronchodilators in patients with HF. Improvements in pulmonary function,[4-10] dyspnea,[10] and exercise performance[7] have been reported. Some investigators have even observed an increase of mean forced expiratory volume in 1 s (FEV_1) greater than 200 mL and 12% in patients with HF,[6, 8, 9] especially in those with AO,[8] left ventricular systolic dysfunction (LVSD),[9] and during acute decompensation of HF.[6] However, not all could confirm these findings.[7, 10-14] Contrasting results across the studies might be attributed to the small number of patients studied and to the differences in study population, bronchodilators used, and definition of bronchodilator responsiveness (BDR).

The purpose of this study was to evaluate the effect of maximal bronchodilation with combined inhaled salbutamol and ipratropium bromide on pulmonary function and dyspnea in patients with chronic HF. In addition, we determined the proportion of patients with significant BDR (i.e. responder), defined as post-bronchodilator (BD) increase in FEV_1 greater than 200 mL and 12% from the baseline value.[15]

Methods

Study design and participants

In this retrospective observational study we analyzed data of chronic HF[16] outpatients with left ventricular ejection fraction (LVEF) below 40%, New York Heart Association (NYHA) class I to IV, and age ≥ 18 years. These patients were recruited prospectively in another study from two outpatient cardiology departments of a large general hospital in The Netherlands between October 2009 and December 2010 for the purpose of evaluating the prevalence of chronic obstructive pulmonary disease (COPD) and pulmonary function impairment in chronic HF (ClinicalTrials.gov Identifier NCT01429376). Only patients with both pre- and post-BD spirometry results were included in the current study. Patients who were not able to cooperate or undergo spirometry or had a history of asthma[17] were excluded. Other exclusion criteria were malignancy with a bad prognosis (survival < 6 months) and participation in another study. In addition, patients with a history of COPD[15] or not further specified obstructive lung disease (OLD) were excluded from the current study. Echocardiography was performed in patients without a recent (≤ 6 months) echocardiography to confirm persisting LVSD.

Patients were classified as having stable HF in the absence of hospitalization due to HF ≤ 3 months, change in diuretics ≤ 1 month, ≥ 3% weight gain ≤ 3 days, and > 50% increase of N-terminal pro-B natriuretic peptide (NT-pro-BNP) ≤ 1 month (baseline NT-pro-BNP ≥ 100 pmol/L) or > 100 pmol/L increase of NT-pro-BNP ≤ 1 month (baseline NT-pro-BNP < 100 pmol/L).[18]

Measurements and data collection

At baseline, a first blood sample was taken for the measurement of NT-pro-BNP. One month later, the participants visited the hospital for an interview with the investigator and several examinations, including height and weight measurement, spirometry and a 10-point Borg dyspnea score[19] before and after bronchodilators, a chest radiograph, and a second blood sample (NT-pro-BNP). Additional data were collected from medical records and personal interviews. Smoking status was defined as never (< 100 cigarettes in a lifetime), former (≥ 3 months ago), or current smoker (< 3 months). Smoking pack-years (PY) were based only on the tobacco cigarette history and one PY was defined as smoking 20 cigarettes a day for 1 year.

Pulmonary function tests

Participants performed spirometry (MasterLab Pro, Jaeger, Würzburg, Germany) before and 30 minutes after inhalation of four doses of 100 μg aerosolized salbutamol and four doses of 20 μg aerosolized ipratropium bromide via Volumatic spacer. Beta-blockers were not discontinued prior to testing. Spirometry was performed by trained and certified operators using standard techniques and according to European Respiratory Society standards for acceptability and reproducibility.[20] Reference values of the European Community for Coal and Steel were used.[20] AO was defined as the ratio of FEV_1 to forced vital capacity (FEV_1/FVC) < 0.7.[15]

Chest radiographs

Standard posteroanterior and lateral chest radiographs were performed and evaluated on the presence or absence of congestion: alveolar edema, pleural effusion, Kerley-B lines, and/or redistribution of pulmonary blood flow.

Ethical considerations

The study was approved by the regional Research Ethics Committee Arnhem-Nijmegen in The Netherlands. All patients gave written informed consent.

Statistical analysis

Descriptive data are presented as mean ± SD or as number (%). Differences between pre- and post-BD spirometry results were analyzed with the dependent t-test and the Wilcoxon signed-rank test was used to analyze the effect of bronchodilators on

dyspnea. Relationships between improvements in pulmonary function and LVEF, baseline pulmonary function, and changes in Borg score were examined using the Pearson's or Spearman's correlation coefficient tests, as appropriate. Differences in BDR between three groups of patients were examined with independent analysis of variance; group 1: patients with persistent AO after bronchodilation, group 2: patients with fully reversible AO, group 3: patients without AO. Post hoc analyses were performed using Fisher's LSD procedure while Games-Howell procedure was used when the assumption of homogeneity of variance was not met. Comparisons between two groups of patients were analyzed using an independent t-test or Mann-Whitney U test for continuous variables and a chi-square or Fisher's exact test for categorical variables, as appropriate (not all data shown). Statistical analyses were performed using the Statistical Package for Social Science version 15.0. All statistical tests were two-sided and a p-value < 0.05 was considered significant.

Results

Patient characteristics

Of the 234 patients recruited in the prospective study, 154 had both pre- and post-BD spirometry results of whom 38 had a history of COPD or not further specified OLD. The remaining 116 patients (50%) were selected for the current study (Figure 1). Table 1 shows the characteristics of these patients. Mean age was 70 ± 10 years and 83% were men. LVEF was 28 ± 7% and 86% had stable chronic HF. Only 14% had signs of congestion on chest radiograph. Over 60% had an ischemic etiology of HF. Other causes of HF were idiopathic (18%), hypertension (6%), valve disease (9%), tachycardiomyopathy (2%), and other (3%). The majority had NYHA class II (72%) and most patients were current or former smokers (81%). Symptoms of dyspnea at rest and/or on exertion were present in 80%.

Bronchodilator responsiveness

AO was present in 64 of 116 (55.2%) patients before administration of inhaled bronchodilators. Of these patients, 39 (60.9%) had persistent AO after bronchodilation. Thus, bronchodilators fully reversed AO in 25 of 64 (39.1%) patients.

Significant improvements in pulmonary function were noted in all spirometric indices except for FVC and inspiratory capacity (IC) after bronchodilation (Table 2). Mean absolute and percent baseline changes in FEV_1 were 0.15 ± 0.14L and 6.1 ± 5.9%, respectively. Corresponding changes for FVC and IC were 0.04 ± 0.23L (1.4 ± 6.5%) and 0.06 ± 0.37L (2.5 ± 13.0%), respectively. Figure 2 shows mean absolute and percent baseline changes in FEV_1, FVC, and IC according to three groups of patients:

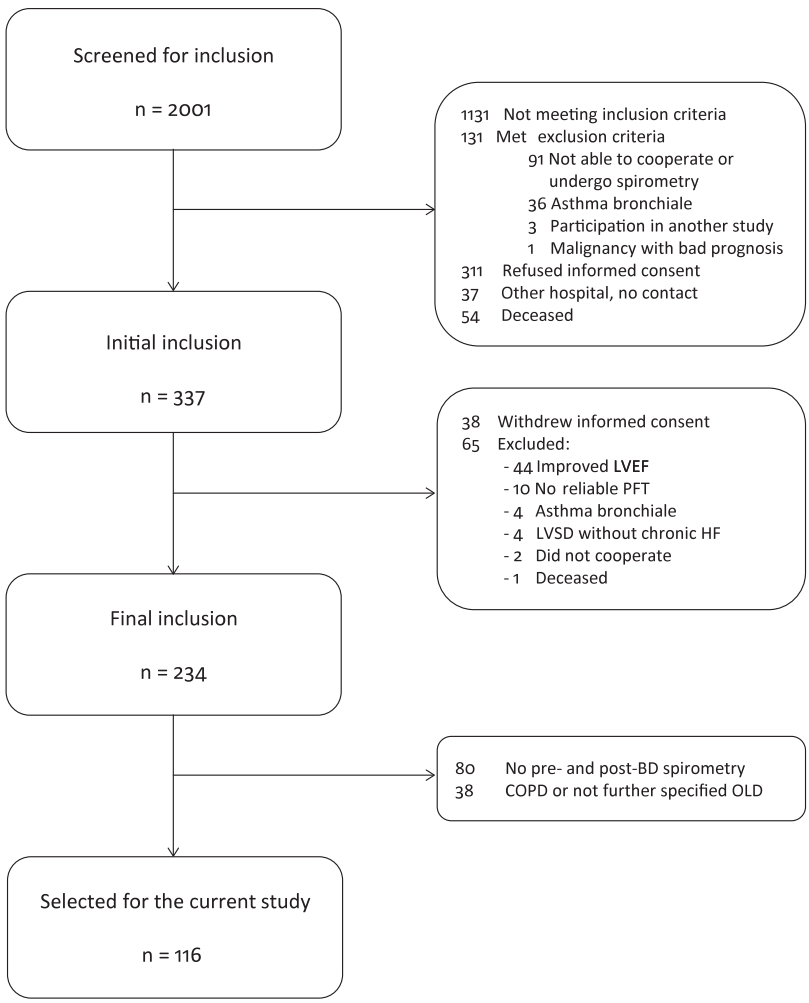

Figure 1 Flow-diagram of screening and final selection of study participants. Abbreviations: COPD, chronic obstructive pulmonary disease; HF, heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; OLD, obstructive lung disease; PFT, pulmonary function tests; pre-/post-BD, pre-/post-bronchodilators.

Table 1 Characteristics of the patients.

Characteristics	n = 116
Age, years	70 ± 10
Male sex, n (%)	96 (82.8)
BMI, kg/m^2	28 ± 4
LVEF, %	28 ± 7
NYHA class, n (%)	
NYHA I	21 (18.1)
NYHA II	83 (71.6)
NYHA III	12 (10.3)
Stable heart failure, n (%)	100 (86.2)
Congestion, n (%)	16 (13.8)
Ischemic etiology, n (%)	72 (62.1)
Dyspnea, n (%)	93 (80.2)
Smoking history, n (%)	
Non-smoker	22 (19.0)
Current smoker	17 (14.7)
Former smoker	77 (66.4)
PY, years	19 ± 20
Co-morbidity, n (%)	
Myocardial infarction	73 (62.9)
Atrial fibrillation	47 (40.5)
Hypertension	50 (43.1)
Diabetes mellitus	24 (20.7)
PCI/CABG	50 (43.1)
CRT/ICD	39 (33.6)
Cardiac medication, n (%)	
ACE-I/ARB	109 (94.0)
Beta-blockers	105 (90.5)
Selective	56 (48.3)
Non-selective	49 (42.2)
Diuretics	95 (81.9)
Aldosterone-antagonists	46 (39.7)
Digoxin	14 (12.1)
Nitrates	14 (12.1)
Calcium-antagonists	8 (6.9)
Laboratory data	
NT-pro-BNP1, pmol/L	271 ± 363
NT-pro-BNP2, pmol/L	296 ± 432

Data are presented as mean ± SD and number (%). Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CRT/ICD, cardiac resynchronization therapy/implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B natriuretic peptide; NYHA, New York Heart Association; PY, pack-years; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting.

Table 2 Results of spirometry pre- and post-bronchodilator.

Spirometry	Pre-BD (n = 116)	Post-BD (n = 116)	p-value
FEV_1, L	2.6 ± 0.7	2.8 ± 0.7	<0.001
FEV_1, % pred.	91 ± 18	96 ± 18	<0.001
FVC, L	3.9 ± 1.0	3.9 ± 1.0	0.066
FVC, % pred.	104 ± 18	105 ± 18	0.066
FEV_1/FVC, %	68 ± 8	71 ± 8	<0.001
PEF, L/s	8.1 ± 2.3	8.6 ± 2.3	<0.001
PEF, % pred.	107 ± 24	113 ± 24	<0.001
IC, L	3.0 ± 0.8	3.1 ± 0.8	0.093
IC, % pred.	104 ± 20	106 ± 22	0.068
FEF_{50}, L/s	2.2 ± 1.0	2.6 ± 1.2	<0.001
FEF_{50}, % pred.	56 ± 25	66 ± 28	<0.001

Data are presented as mean ± SD. Pulmonary function data, with exception of FEV_1/FVC, are expressed as absolute values and as percent predicted, based on age, height, and sex**.** Abbreviations: FEF_{50}, forced expiratory flow at 50% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; PEF, peak expiratory flow; pre-/post-BD, pre- or post-bronchodilators.

those with persistent AO after bronchodilation (n = 39), those with fully reversible AO (n = 25), and those without AO both before and after bronchodilation (n = 52). Both absolute and percent baseline changes in FEV_1 were more pronounced in patients with persistent AO compared to those without AO ($p < 0.05$). Absolute and percent baseline changes in FVC were different across the groups ($p < 0.05$). An increase of 0.15 ± 0.25 mL (4.5 ± 8.1%) in mean FVC was observed in patients with persistent AO. On the other hand, a decrease of 0.09 ± 0.15 mL (2.4 ± 3.4%) was noted in the group with fully reversible AO, while patients without AO did not show a significant change in FVC. Changes in IC were not significantly different across the three groups.

Significant BDR of FEV_1 (> 200 mL and > 12%) was noted in 12.1% of the entire study population (Table 3). Patients with persisting AO and those with fully reversible AO had significant BDR of FEV_1 more often than patients without AO (23.1% and 16.0% versus 1.9%, respectively, $p < 0.05$).

Improvement in FEV_1, especially percent improvement from baseline, correlated weakly to moderately with pre-BD pulmonary function (Table 4). There was no significant correlation between improvement in FEV_1 and LVEF. Patients using non-selective

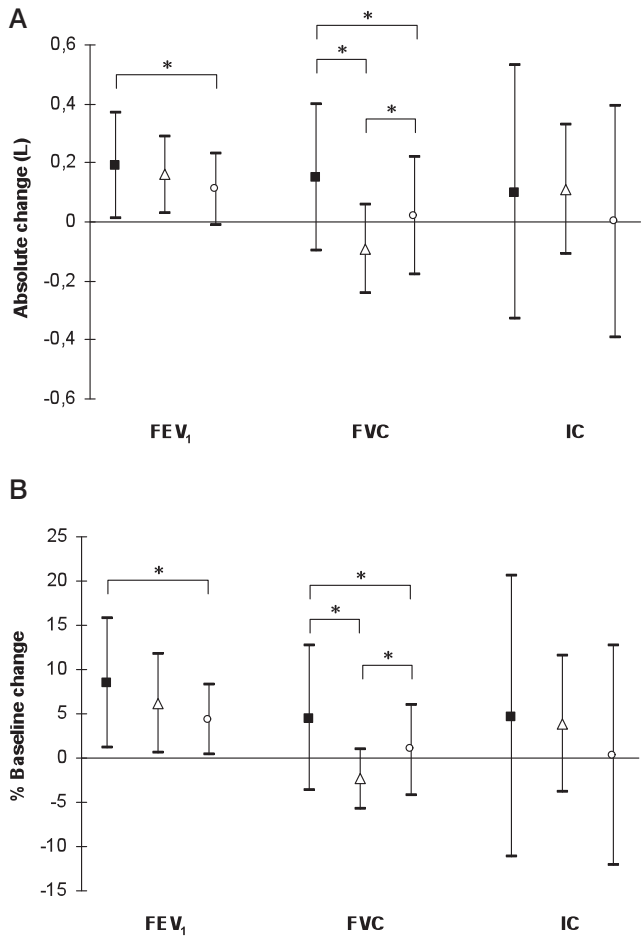

Figure 2 Absolute (A) and percent baseline changes (B) in FEV_1, FVC, and IC after bronchodilation. Data are presented as mean ± SD. ■ Patients with persistent airway obstruction (AO); Δ patients with fully reversible AO; o patients without AO. *p-value < 0.05. Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity.

beta-blockers showed less reversibility of IC and forced expiratory flow at 50% of FVC (FEF_{50}) than those using selective beta-blockers (0.0 ± 9.9% versus 5.2 ± 14.1%, $p = 0.034$, and 13.5 ± 17.3% versus 23.8 ± 23.9%, $p = 0.014$, respectively). The reversibility of other pulmonary function variables were similar between the groups. Also, baseline pulmonary function measurements and the prevalence of AO before

Table 3 Patterns of bronchodilator responsiveness.

Patient groups	No.	Significant BDR, n (%)
All	116	14 (12.1)
Persistent AO	39	9 (23.1)
Fully reversible AO	25	4 (16.0)
No AO	52	1 (1.9)*†

Data are presented as number (%). Abbreviations: AO, airway obstruction; BDR, bronchodilator responsiveness. *p-value < 0.05 versus patients with persistent AO. †p-value < 0.05 versus patients with fully reversible AO.

Table 4 Relationship between improvement in FEV_1 after bronchodilation and pre-bronchodilator pulmonary function.

	Absolute improvement in FEV_1 (n = 116)		% Baseline improvement in FEV_1 (n = 116)	
	Correlation coefficient	p-value	Correlation coefficient	p-value
FEV_1, L	0.025	0.794	-0.234	0.012
FEV_1, % pred.	-0.216	0.020	-0.402	<0.001
FVC, L	0.152	0.103	-0.083	0.374
FVC, % pred.	-0.083	0.376	-0.232	0.012
FEV_1/FVC, %	-0.248	0.007	-0.325	<0.001
PEF, L/s	-0.085	0.364	-0.310	0.001
PEF, % pred.	-0.243	0.008	-0.432	<0.001
IC, L	0.240	0.009	0.028	0.762
IC, % pred.	0.036	0.704	-0.080	0.394
FEF_{50}, L/s	-0.111	0.236	-0.301	0.001
FEF_{50}, % pred.	-0.176	0.058	-0.337	<0.001

Abbreviations: FEF_{50}, forced expiratory flow at 50% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; PEF, peak expiratory flow.

and after bronchodilation were not affected by the type of beta-blocker used. Stability of chronic HF, congestion on chest radiograph, a smoking history, and a history of atrial fibrillation did not impact the magnitude of BDR. However, patients with pulmonary congestion did have more impaired pulmonary function (Table 5) and were more obstructed after bronchodilation than those without pulmonary congestion

Table 5 Results of spirometry pre- and post-bronchodilator in patients with and without pulmonary congestion.

Spirometry	Pre-BD			Post-BD		
	Congestion – (n = 100)	Congestion + (n = 16)	p-value	Congestion – (n = 100)	Congestion + (n = 16)	p-value
FEV_1, L	2.7 ± 0.7	2.2 ± 0.7	0.014	2.8 ± 0.7	2.3 ± 0.7	0.010
FEV_1, % pred.	93 ± 18	78 ± 17	0.001	98 ± 17	82 ± 17	0.001
FVC, L	3.9 ± 0.9	3.4 ± 1.1	0.067	4.0 ± 0.9	3.4 ± 1.1	0.035
FVC, % pred.	106 ± 18	92 ± 16	0.005	107 ± 17	91 ± 17	0.001
FEV_1/FVC, %	69 ± 8	65 ± 6	0.106	72 ± 8	69 ± 7	0.217
PEF, L/s	8.3 ± 2.2	7.2 ± 2.6	0.088	8.8 ± 2.2	7.5 ± 2.4	0.039
PEF, % pred.	109 ± 24	95 ± 27	0.037	115 ± 23	99 ± 23	0.008
IC, L	3.1 ± 0.8	2.5 ± 0.6	0.007	3.1 ± 0.8	2.5 ± 0.7	0.005
IC, % pred.	106 ± 20	88 ± 16	0.001	109 ± 21	88 ± 16	<0.001
FEF_{50}, L/s	2.4 ± 1.0	1.5 ± 0.7	0.004	2.8 ± 1.2	1.9 ± 0.8	0.004
FEF_{50}, % pred.	58 ± 25	39 ± 18	0.003	69 ± 28	47 ± 21	0.003

Data are presented as mean ± SD. Pulmonary function data, with exception of FEV_1/FVC, are expressed as absolute values and as percent predicted, based on age, height, and sex. Abbreviations: FEF_{50}, forced expiratory flow at 50% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; PEF, peak expiratory flow; pre-/post-BD, pre- or post-bronchodilators.

(56.3% versus 30%, p = 0.039). Current and former smokers had significantly lower pre- and post-BD FEV_1/FVC ratio than non-smokers (67 ± 8% versus 72 ± 7%, p = 0.022, and 70 ± 8% versus 75 ± 7%, p = 0.011, respectively), but the prevalence of pre- and post-BD AO was not significantly different between the groups (pre-BD 57.4% versus 45.5%, p = 0.309, and post-BD 37.2% versus 18.2%, p = 0.089, respectively). Also, the proportion of patients with completely reversible airway obstruction after bronchodilation was not significantly different between current/former smokers and non-smokers (35% versus 60%, p = 0.170).

Clinically small, albeit statistically significant improvements in the Borg dyspnea score were observed after bronchodilation in the entire group (0.7 ± 1.2 versus 0.9 ± 1.3, p = 0.002). Improvement in Borg score was not significantly different between responders or non-responders and it was not correlated to the improvement of FEV_1. Also, the type of beta-blocker used, congestion on chest radiograph, a smoking history, and a history of atrial fibrillation did not impact the magnitude of Borg score improvement.

Discussion

The results of this study confirm that inhaled bronchodilators have the potential to improve pulmonary function in patients with chronic HF, especially in those with AO. Importantly, full reversal of AO was seen in approximately 40% of patients who had pre-BD AO. However, improvement in dyspnea at rest after bronchodilation was small and did not correlate to improvement in pulmonary function.

Our findings agree with the notion that airway narrowing associated with HF has a reversible component, as almost 40% of patients without a history of COPD or asthma who had pre-BD AO fully recovered after bronchodilation. The bronchodilatory effect is most probably explained by a reduction in the increased bronchial tone which may contribute to AO in patients with HF. Also, acutely delivered beta-agonists may act by improving cardiovascular hemodynamics and resorption of pulmonary edema.[21] However, considering the speed with which bronchodilation took place and the fact that most patients were not congested on chest radiograph, this was likely not the main mechanism of action.

Similar rates of fully reversible AO after bronchodilator testing were reported in a population-based survey with reductions in AO prevalence between 32% and 39%, depending on the definition used to describe airflow obstruction.[22] Consistent with the findings of that study we observed an increase in mean FEV_1 and a decrease in

mean FVC in the fully reversible group of patients while the group with persistent AO did in fact show an increase in both parameters. This may explain why the group with persistent AO maintains a low ratio of FEV_1/FVC after bronchodilation while this ratio normalizes in the group with reversible AO. We cannot exclude the possibility that some of the patients with complete reversal of AO in our study may have had previously undiagnosed asthma, as new-onset asthma may occur at any age and is often underrecognised or misdiagnosed in the elderly.[23] However, there was no indication of asthma based on symptoms and physical examination in these patients except for one patient who was diagnosed with asthma after having participated in our study. Excluding this patient from the analysis still yielded similar rates of fully reversible AO (38.1%).

The incomplete reversal of AO in other patients may be due to irreversible anatomical alterations of the bronchial wall. In fact, AO in HF has been attributed to increased thickness of the airway wall due to bronchial mucosal swelling, peribronchial edema, and fibrosis. In addition, alveolar fluid accumulation may have contributed.[2] Although most patients were not congested on chest radiograph and pulmonary congestion did not influence the magnitude of BDR, occult congestion with small airways compression may still have been present. In support, although pulmonary function improved with treatment for cardiac decompensation in the study of Light and George,[13] a great number of patients without a history of chronic obstructive lung disease still had evidence of airway obstruction. In the same study, airway obstruction did not improve after the administration of nebulized bronchodilators in the majority of the patients. Another plausible explanation for the persistent AO could be previously undiagnosed pulmonary disease, such as COPD, which is underrecognized in patients with HF.[14] In support of this explanation, our patients with persistent AO without a previous diagnosis of COPD had comparable BDR to 38 chronic HF patients with known COPD of similar age, gender, and LVEF (data not shown). Thus, patients with post-BD AO, irrespective of a previous diagnosis of COPD, might similarly benefit from bronchodilators. On the other hand, although smoking, which is a major risk factor for COPD, was associated with lower FEV_1/FVC ratio, the prevalence of post-BD AO was not significantly different between current/former smokers and non-smokers. This may be, however, the result of a small number of non-smokers included in our study. Other differential diagnosis of fixed AO should also be considered, such as bronchiectases and late-onset asthma.[23] Finally, considering the physiological decline of the FEV_1/FVC ratio with age, the low ratio of FEV_1/FVC below 0.7 may still be normal for the age of the patients when using the lower limit of normal to define AO.[24]

An interesting finding of our study was that the use of non-selective beta-blockers instead of selective beta-blockers resulted in less reversibility of IC and FEF_{50}. This finding is in line with prior evidence that non-selective beta-blockers may antagonize beta-agonists.[25] In contrast, baseline pulmonary function, the prevalence of AO, and improvement of dyspnea were not affected by the type of beta-blocker used.

Prior research concerning the beneficial effects of bronchodilators in patients with HF is scarce. Improvements in pulmonary function,[4-10] dyspnea,[10] and exercise performance[7] have been reported. Some investigators have even observed an increase of mean FEV_1 greater than 200 mL and 12% in patients with HF,[6, 8, 9] especially in those with AO,[8] LVSD,[9] and during acute decompensation of HF.[6] However, contrasting results have also been published. In the study of Witte et al.[10] nebulized salbutamol (5 mg) and ipratropium bromide (0.5 mg) reduced peripheral airways resistance and breathlessness during exercise in twelve patients with stable chronic HF and increased measures of compliance. However, spirometry was not altered significantly and exercise capacity did not improve with bronchodilation. Similarly, treatment with three weeks of salbutamol (slow-release 8 mg twice daily) did not improve exercise capacity or spirometric measurements in a randomized placebo-controlled trial of twelve chronic HF patients, although respiratory muscle strength did increase.[11] Furthermore, there were no improvements in symptom scores as measured with the Minnesota living with HF questionnaire and fatigue dyspnea index in the same study. In addition, pre-treatment with nebulized albuterol (2.5 mg) and ipratropium bromide (0.5 mg) had only minor effects on spirometric values at rest and did not influence exercise performance and visual analogue score for dyspnea at peak exercise in a randomized, double-blind crossover study of nine patients with HF.[12] Furthermore, although a small but significant increase in maximal exercise capacity and spirometric indices was seen after pre-treatment with nebulized salbutamol (5 mg) and with ipratropium bromide (0.5 mg) in a randomized double-blind study of ten patients with chronic HF, both bronchodilators had no effect on the perception of dypnoea, as measured by a visual analogue scale.[7] Finally, significant reversibility, defined as more than 400 mL increase in FEV_1 after inhalation of 0.2 mg fenoterol and 40 μg ipratropium, could not be demonstrated in 131 patients admitted with HF in a prospective substudy,[14] whereas only four of eighteen patients with congestive HF had greater than 10% improvement in FEV_1 after bronchodilation in another study.[13] Contrasting results across the studies might be attributed to the small number of patients studied and to the differences in study population, bronchodilators used, and definition of BDR.

There is no consensus about the drug, dose, or mode of administering a bronchodilator to test BDR.[24] Since BDR may differ with the bronchodilator used, we sought to obtain maximal bronchodilation by combining two bronchodilators with different mechanisms of action. In addition, we used the most recent criteria to define significant BDR.[15] Whether the presence or absence of significant BDR in patients with chronic HF predicts prognostic outcome and clinical response to bronchodilators has not been investigated before and needs further research. The small improvement in dyspnea after bronchodilation was not significantly different between responders or non-responders in our patients with chronic HF. Similarly, BDR status did not predict clinical benefit of bronchodilators in patients with COPD in the UPLIFT trial.[26]

Clinical implications

Based on our results, inhaled bronchodilators may have an additional role in the management of patients with chronic HF because of their potential to improve pulmonary function, especially in those with AO. This may contribute to decrease in perceived dyspnea and exercise limitation as demonstrated by others.[7, 10] Although post-BD improvements in resting dyspnea were clinically small and not related to improvements in pulmonary function in this study, greater symptomatic relief might be possible in more symptomatic patients and with longer duration of treatment. Further randomized-control trials are needed to examine the clinical benefits as well as potential adverse events of bronchodilators in the treatment of chronic HF.[27] Concerns have been raised regarding the cardiovascular safety profile of these drugs.[25, 27-30] Recently, reassuring cardiovascular safety data have been reported on long-acting anticholinergic bronchodilator tiotropium (HandiHaler) in patients with COPD.[31, 32] However, HF patients are usually excluded from clinical trials and the impact of bronchodilators on outcomes has never been prospectively evaluated in patients with HF.[27] Observational studies showed worse outcomes with bronchodilator use in patients with HF, including increased risk of HF hospitalization, increased mortality rates, in-hospital mechanical ventilation, intravenous vasodilator use, and major cardiovascular events. Possible mechanisms for adverse cardiovascular outcomes are arrythmogenesis, ischemia, hypoxemia, inflammation, cardiac remodeling, metabolic alterations (hypokalemia), and/or attenuation of beta-blocker benefits.[25, 27] In addition, physicians must be wary of diminished hepatic metabolism of beta-agonists in patients with HF, leading to prolonged plasma half-life and accumulation with repeated doses.[5]

Methodological limitations of most studies require further investigation of reported adverse events.[25, 27] Until then, bronchodilators, in particular beta-agonists, must be used with caution in patients with cardiac disease.

Study limitations

This retrospective observational study has several limitations that need to be addressed. First, it is important to realize that results may not be applicable to all patients with chronic HF, since we did not include patients with preserved systolic function, who seem to have less impaired pulmonary function.[9] Therefore, the bronchodilator effect may have been greater in our patients with decreased systolic function. Also, patients with more severe and unstable HF could have been underrepresented in this study because of inability to participate. There is evidence to indicate greater bronchodilator effect during acute exacerbation of heart failure,[6] although both stability of HF and congestion on chest radiograph did not impact the magnitude of BDR in the current study. Second, since we did not measure the effects of salbutamol and ipratropium bromide separately, comparison between both agents was not possible. It is not unlikely that some patients may respond more to salbutamol than ipratropium bromide and vice versa. However, similar improvements in FEV_1 after salbutamol or ipratropium were noticed by Uren et al., although peak expiratory flow rates increased more with salbutamol.[7] Third, we did not perform spirometry following placebo inhalations. However, no significant changes with placebo were observed in other studies,[6, 7] suggesting genuine effect of bronchodilators. Fourth, since we did not include a control group, we could not establish whether improvements in pulmonary function observed in patients with chronic HF are a reflection of the response observed in normal subjects. However, one in five patients with pre-BD AO had a significant BDR of FEV_1 which is considered to exceed spontaneous variability, response to placebo inhalations, and the response observed in healthy individuals. Fifth, we did not measure the effect of bronchodilators on airway resistance. Patients who do not improve on spirometry may still benefit from bronchodilators due to a decrease in airway resistance.[10] Also, we did not measure the effect of bronchodilators on heart rate and blood pressure. However, no cardiac adverse effects of bronchodilators such as palpitations and angina were reported during the study. Finally, it is important to realize that our findings are based on a single measurement of BDR and results may differ with serial measurements.[26]

Conclusion

In conclusion, inhaled bronchodilators may have an additional role in the management of patients with chronic HF because of their potential to improve pulmonary function, especially in those with AO. Despite excluding patients with a history of COPD or asthma, more than half of the chronic HF population studied had pre-BD AO that was fully reversible in approximately 40% of these patients. However, the clinical usefulness and potential adverse events of bronchodilators in the treatment of chronic HF need to be further established in randomized placebo-controlled trials.

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Comment on the letter to the editor entitled 'Bronchodilator responsiveness in patients with chronic heart failure'

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Reply to letter to the editor

We thank Dr. Alkhuja and colleagues for their comments on our recent article 'Bronchodilator responsiveness in patients with chronic heart failure'.[1] They stressed the presence of airway obstruction (AO) and the role of bronchial hyperreactivity / hyperresponsiveness in patients with pulmonary congestive changes secondary to heart failure (HF) in the absence of chronic obstructive pulmonary disease (COPD). They suggested a lower threshold to the administration of inhaled bronchodilators in patients with heart failure without COPD, because of their potential to completely reverse the bronchial obstruction. Finally, they mentioned that the high prevalence of current or former smokers (81%) in our study may explain the presence of AO and the bronchodilator response found in our group of patients.

Several factors have been implied to play a role in the etiology of AO in patients with HF, including the effects of HF itself on pulmonary function as well as confounding influences such as smoking which may lead to COPD. In addition, a careful history taking, physical examination, and additional investigation should be carried out to exclude other co-morbidities that may be the cause of AO, such as bronchial asthma and bronchiectasis.

AO due to HF itself has been attributed to several factors such as alveolar fluid accumulation, bronchial mucosal swelling, peribronchial edema and fibrosis, squamous metaplasia of bronchial epithelial cells induces by transforming growth factor-ß from the failing heart, geometric decrease in airway size from reduction in lung volume, abnormalities of autonomic control, neural (vagal reflex) bronchoconstriction secondary to pulmonary edema, and bronchial hyperresponsiveness which is thought to be mediated at least in part by dilatation of the bronchial vessels.[2-5] Brenner et al.[6] found transient AO to be an important clinical feature of systolic HF, as AO resolved in 24 of 51 (47%) patients under more stable condition six months after discharge from the hospital. This finding is supported by other studies showing that AO due to HF may be partially or completely reversible by means of cardiac therapy alone.[7, 8] Thus, the first step in treating AO in patients with HF should include optimizing treatment directed at the failing heart to achieve a more compensated state. Patients with chronic HF with persisting AO under maximal treatment for their HF may benefit from inhaled bronchodilators as additional treatment because of their potential to improve pulmonary function,[1] dyspnea,[1] and exercise performance.[9] As an example, in our subgroup of patients with stable chronic HF without pulmonary congestion (n = 90) bronchodilators fully reversed AO in 21 of 48 patients (43.8%) who had AO before administration of bronchodilators. Mean absolute and percent baseline changes in FEV_1 were 0.16 ± 0.15L and 6.4 ± 5.9%, respectively. However, contrasting results

have been published regarding the beneficial effect of bronchodilators in patients with HF[1] and concerns have been raised regarding the cardiovascular safety profile of these drugs.[10-14] Therefore, it is our belief that further randomized-control trials are needed to examine the clinical benefits as well as potential adverse events of bronchodilators in the treatment of HF before advising the routine use of bronchodilators in patients with HF.[11]

Finally, although patients with pulmonary congestion as well as current and former smokers did have more impaired pulmonary function, both pulmonary congestion and a smoking history did not impact the magnitude of bronchodilator responsiveness in our study population (Table 1 and 2). In contrast, ipratropium produced a far better bronchodilation during acute decompensation than after intensive treatment for heart failure in another study.[15] The authors hypothesized that this finding could be explained by an increase in cholinergic bronchial tone due to lung edema or altered physical properties of the bronchial wall (more edematous) in HF which could explain why an equal smooth muscle relaxation induced by ipratropium would result in a greater bronchodilating effect during acute decompensation. Future research should focus on the value of bronchodilators in different subgroups of patients (acute decompensated versus chronic compensated HF, non-smokers versus current and former smokers, systolic HF versus patients with preserved systolic function, and so on).

Table 1 Bronchodilator responsiveness in patients with and without pulmonary congestion.

Bronchodilator responsiveness	Congestion – (n = 100)	Congestion + (n = 16)	p-value
Absolute change in FEV_1, L	0.15 ± 0.14	0.12 ± 0.16	0.427
% Baseline change in FEV_1	6.1 ± 5.7	5.8 ± 6.8	0.844
Absolute change in FVC, L	0.05 ± 0.22	-0.02 ± 0.26	0.255
% Baseline change in FVC	1.6 ± 6.4	-0.1 ± 6.7	0.319
% Baseline change in FEV_1/FVC	3.0 ± 3.6	3.9 ± 3.4	0.387

Data are presented as mean ± SD. Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2 Bronchodilator responsiveness in non-smokers versus current or former smokers.

Bronchodilator responsiveness	NS (n = 22)	CS/FS (n = 94)	p-value
Absolute change in FEV_1, L	0.16 ± 0.13	0.15 ± 0.15	0.841
% Baseline change in FEV_1	6.9 ± 6.0	5.9 ± 5.9	0.474
Absolute change in FVC, L	0.04 ± 0.18	0.04 ± 0.24	0.931
% Baseline change in FVC	2.0 ± 7.4	1.2 ± 6.3	0.627
% Baseline change in FEV_1/FVC	3.5 ± 4.1	3.1 ± 3.5	0.567

Data are presented as mean ± SD. Abbreviations: CS, current smokers; FEV_1, forced expiratory volume in 1 s; FS, former smokers; FVC, forced vital capacity; NS, non-smokers.

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Comment on the letter to the editor entitled 'Heart failure: not only reduced left ventricular ejection fraction but also reserved ejection fraction!

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Reply to letter to the editor

We thank Dr. Aydogan and colleagues for their comments on our recent article 'Bronchodilator responsiveness in patients with chronic heart failure'.[1] Main results of our study were the improvement in almost all spirometric measurements of pulmonary function with inhaled bronchodilators in patients with chronic heart failure (HF) with left ventricular systolic dysfunction (LVSD), especially in those with airway obstruction. Importantly, full reversal of airway obstruction was seen in approximately 40% of patients who had pre-bronchodilator airway obstruction. However, improvement in Borg dyspnea scores at rest after bronchodilation was small (0.7 ± 1.2 versus 0.9 ± 1.3, $p = 0.002$) and did not correlate to improvement in pulmonary function. Dr. Aydogan and colleagues suggested that undiagnosed or untreated pulmonary hypertension may be the reason for this result. They also noticed that the results of our study may be different in HF patients with diastolic HF.

Indeed, up to 60% of patients with severe LVSD and up to 70% of patients with isolated LV diastolic dysfunction may present with pulmonary hypertension which may be one of the reasons why patients with chronic HF complain of breathlessness.[2] However, other potential factors, alone or in combination, may also explain dyspnea experienced by these patients, including cardiac dysfunction, pulmonary function impairment (airway obstruction, restriction, diffusion impairment, decreased lung compliance, ventilation/perfusion mismatch), respiratory muscle dysfunction, expansion of the chest wall leading to activation of chest wall position sensors, direct stimulation of nerve endings by vascular distention and interstitial edema, and co-morbidities such as anemia and previously undiagnosed pulmonary disease.[3, 4-5] This multi-factorial etiology of dyspnea in patients with chronic HF may explain the only small improvement in dyspnea despite significant improvement in pulmonary function in our study. However, we believe that the main reason for this rather small improvement in dyspnea and the lack of correlation with improvement in pulmonary function was probably the fact that the majority of our patients had stable chronic HF without signs of pulmonary congestions and therefore did not report symptoms of dyspnea at rest (67.2% had Borg scores between 0 and 0.5, mean Borg score 0.9 ± 1.3). Greater symptomatic relief might be possible in more symptomatic patients and with longer duration of treatment. In addition, selection of other outcome variables such as other dyspnea scales or exercise capacity may lead to different results. There is unfortunately no consensus on which tool should be used to measure breathlessness severity, despite breathlessness being an important limiting problem for patients with chronic HF.[6] Also, since we did not measure the effect of bronchodilators on airway resistance, it remains unknown whether improvement in airway resistance correlates to improvement in dyspnea.

Unfortunately, we do not have data on echocardiographic estimates of pulmonary artery pressure (PAP) in all of the patients studied. Not all patients underwent echocardiography during this study, as it was performed only in patients without a recent (≤ 6 months) echocardiography to confirm persisting LVSD. Consequently, estimates of PAP obtained a few months before the study may not be representative of PAP during the study, as PAP depends on the actual volemic state of HF. In addition, echocardiography was not performed before and after bronchodilation in the current study and it therefore remains unknown whether bronchodilators may improve dyspnea by decreasing PAP. Evidence shows that acutely delivered beta-2 agonists in patients with chronic HF increase cardiac output/index and decrease systemic vascular resistance and left-sided cardiac filling pressures due to a combination of afterload reduction through vasodilatation and enhanced contractile state.[7] Moreover, beta-2 agonists are known to decrease pulmonary edema in animal studies of HF and acute lung injury by increasing transepithelial sodium and chloride transport.[7] Thus these mechanisms, in addition to the bronchodilator effect of beta-2 agonists, provide a theoretical benefit of beta-2 agonists to patients with dyspnea due to HF. This hypothesis deserves further investigation.

Finally, as mentioned in the limitation section of our article, the results of our study indeed may not be applicable to all patients with chronic HF, since we did not include patients with preserved systolic function, who seem to have less impaired pulmonary function.[8] Future studies should also focus on HF patients with preserved systolic function.

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CHAPTER 7

Summary

Conclusions

General discussion

Future perspectives

Summary

The aim of this thesis is to provide more insight in the occurrence of COPD and pulmonary function abnormalities using different definitions in patients with CHF. In addition, we aimed to determine under- and overdiagnosis of COPD, the necessity of performing serial PFTs to correctly diagnose COPD, and predictors of pulmonary function abnormalities using different definitions in patients with CHF. Finally, we aimed to evaluate the effect of inhaled bronchodilators on pulmonary function and dyspnea in patients with CHF.

In **chapter 2** we determined the prevalence as well as over- and underdiagnosis of COPD according to the widely used GOLD criteria in 187 outpatients with stable non-congested CHF with LVSD. In addition, we investigated whether serial PFTs are necessary for the correct diagnosis of COPD in this group of patients by using initial as well as confirmatory spirometry three months after treatment with tiotropium in patients with newly diagnosed COPD. We found COPD to be a frequent co-morbidity in patients with CHF, occurring in approximately one-third of the patients. Importantly, it was often unrecognized (19%) or overdiagnosed (32%). Furthermore, we concluded that under stable and euvolemic conditions a confirmatory spirometry is unnecessary for the correct diagnosis of COPD, as it did not change a newly established diagnosis of COPD in the vast majority of patients with CHF.

In **chapter 3** we determined the prevalence of COPD in 187 outpatients with stable non-congested CHF with LVSD according to two definitions of airflow obstruction: the LLN (ATS/ERS guidelines) versus the fixed ratio of $FEV_1/FVC < 0.70$ (GOLD guidelines). We found that the exact definition of airflow obstruction alters COPD prevalence substantially; one fifth, rather than one third, of the patients with CHF had concomitant COPD using the LLN instead of the fixed ratio. Importantly, the LLN seemed to identify clinically more important COPD than the fixed ratio of 0.7; 38% of patients with GOLD-COPD who were potentially misclassified as having COPD ($FEV_1/FVC < 0.7$ but $>$ LLN) did not differ significantly from those without COPD in terms of respiratory symptoms and risk factors for COPD, whereas patients with LLN-COPD did.

In **chapter 4** we investigated the occurrence of pulmonary function abnormalities in 164 outpatients with CHF with LVSD according to the LLN versus conventional cutoff values (i.e. $FEV_1/VC <$ LLN versus $FEV_1/FVC < 0.7$ for airway obstruction, TLCOc $<$ LLN versus $< 80\%$ predicted for diffusion impairment, and TLC $<$ LLN versus $< 80\%$ predicted for restriction). We excluded patients with known pulmonary, pleural, neuromuscular, collagen vascular, or other diseases that could affect pulmonary function. Patients

with a BMI above 35 were excluded from the restriction prevalence analysis. Pulmonary function abnormalities, especially diffusion impairment and airway obstruction, were highly prevalent in patients with CHF, even in a stable and non-congested condition and even though we used the LLN to better account for age. However, prevalence rates varied significantly according to the definition used between 44% and 58% for diffusion impairment and between 26% and 37% for airway obstruction using the LLN versus conventional cutoff values, respectively. In contrast to previous reports, restriction was found to be infrequent in this population of less severe and mainly stable CHF patients without pulmonary congestion, irrespective of the definition used (7% versus 5%, respectively). The conventional cutoff values classified more patients as having diffusion impairment, airway obstruction, or a mixed category compared to the LLN and failed to identify correctly 34% of patients with normal lung function placing them falsely within a pulmonary dysfunction category. Using the conventional cutoff values instead of the LLN led to misclassification of 27% of the patients.

In **chapter 5** we assessed predictors of pulmonary function impairment in 164 outpatients with CHF with LVSD according to the LLN in comparison to conventional cutoff values. The same exclusion criteria as described in chapter 4 were applied. We found that the LLN criterion identified an extra independent predictor of diffusion impairment compared to the 80% predicted value; in addition to BMI, PY, and VA, female gender also turned out to be an independent predictor of diffusion impairment using the LLN. A smoking history of ≥ 10 PY was a significant predictor of diffusion impairment and airway obstruction using the LLN criterion, but not using the conventional cutoff values. However, lowering the cutoff points of conventional criteria to match the more stringent LLN and thus avoid overdiagnosis of diffusion impairment and airway obstruction in the elderly, produced similar results as the LLN. Lower lung volumes were found in patients with pulmonary congestion, cardiomegaly, and a history of CABG.

Finally, in **chapter 6** we evaluated retrospectively the effect of inhaled bronchodilators (combined 400 μg salbutamol and 80 μg ipratropium bromide) on pulmonary function and dyspnea in 116 outpatients with CHF and LVSD. Patients with a history of COPD or asthma were excluded. The results of our study confirmed that inhaled bronchodilators have the potential to improve pulmonary function in patients with CHF, especially in those with airway obstruction. Importantly, full reversal of airway obstruction was seen in approximately 40% of patients without a history of COPD or asthma who had pre-bronchodilator airway obstruction. Significant improvements in pulmonary function were noted in all spirometric indices except for FVC and inspiratory capacity (IC) in the entire study population. Significant BDR of FEV_1 (> 200 mL and > 12% from the baseline value) was noted in 12%. Patients with both

persisting and fully reversible airway obstruction had significant BDR of FEV_1 more often than patients without airway obstruction (23%, 16%, and 2%, respectively). Improvement in dyspnea at rest after bronchodilation was, however, small and did not correlate to improvement in pulmonary function in this selected study population.

Conclusions

- COPD is a frequent co-morbidity in patients with stable non-congested CHF with LVSD, but is often unrecognized or overdiagnosed.

- Spirometry should be used under stable and euvolemic conditions to decrease the burden of undiagnosed or overdiagnosed COPD in patients with CHF. Under these conditions, a confirmatory spirometry is unnecessary, as it does not change a newly established diagnosis of COPD in the vast majority of patients with CHF.

- The exact definition of airflow obstruction alters COPD prevalence substantially; one fifth, rather than one third, of the patients with CHF have concomitant COPD using the LLN instead of the fixed ratio.

- LLN may identify clinically more important COPD than the fixed ratio of 0.7 as patients who are potentially misclassified as having COPD, in contrast to patients with LLN-COPD, do not differ significantly from those without COPD in terms of respiratory symptoms and risk factors for COPD.

- Pulmonary function abnormalities, especially diffusion impairment and airway obstruction, are highly prevalent in patients with CHF.

- Conventional cutoff values classify more patients as having diffusion impairment, airway obstruction, or a mixed category compared to the LLN, leading to mis-classification of 27% of the patients.

- The LLN identifies more predictors of diffusion impairment and airway obstruction compared to the conventional cutoff values. However, lowering the conventional cutoff points to match the more stringent LLN, produces similar results as the LLN.

- Inhaled bronchodilators may have an additional role in the management of patients with CHF because of their potential to improve pulmonary function, especially in those with airway obstruction. Improvement in dyspnea is, however, small and does not correlate to improvement in pulmonary function in this selected study population.

General discussion

1. COPD in CHF

COPD and HF are both common diseases with significant morbidity, mortality, and health care use.[1, 2] The combination of both diseases presents many diagnostic and therapeutic challenges as well as adverse prognostic implications.[1-13] Although the occurrence of HF in patients with COPD has been assessed extensively in prior research, the occurrence of COPD in patients with HF has received much less attention.[4] Moreover, although spirometry is considered to be the gold standard for the diagnosis of COPD, data on the prevalence of COPD based on spirometry in patients with HF are scarce and spirometry remains widely underused.[14] Furthermore, since airway obstruction is a dynamic phenomenon in HF, as it may be present in congestive HF and may disappear with treatment of HF,[15] a careful timing and interpretation of PFTs is required to avoid misdiagnosis and inappropriate treatment of COPD.[1] Ideally, PFTs should be used under stable conditions when clinically euvolemic to establish a valid diagnosis of COPD. However, data on the need of serial pulmonary function measurements to confirm persistent airway obstruction and thus COPD are lacking in patients with stable non-congested CHF. We therefore aimed to determine the prevalence of COPD using spirometry in outpatients with stable CHF without pulmonary congestion. In addition, we investigated whether serial PFTs are necessary for the correct diagnosis of COPD in this group of patients by using initial as well as confirmatory spirometry three months after treatment with tiotropium in patients with newly diagnosed COPD. We observed a high prevalence of COPD (32.1%) according to the GOLD criteria in a well defined subgroup of 187 stable non-congested CHF outpatients with LVSD (i.e. LVEF $<$ 40%) (**chapter 2**). Using a follow-up spirometry after three months of treatment with tiotropium to confirm initial diagnosis of de novo COPD did not change COPD prevalence significantly: 32.6% initially versus 32.1% after three months of follow-up. Importantly, COPD was often unrecognized (19%) or overdiagnosed (32%). Our results support previous findings that COPD frequently coexists with HF (**chapter 1.3, Table 1**), but are in contrast to the study of Brenner et al.[15] who found only 9% of patients with systolic HF to have concomitant COPD, probably explained by the high number of never smokers (46%) included in their study. Several factors might explain the high coexistence of these two diseases, as described in the general introduction. Since spirometry is still underutilized, even in a tertiary-care facility,[14] it seems reasonable to consider routine spirometry testing in patients with CHF to diagnose or rule out COPD, a co-morbidity with important therapeutic and prognostic implications,[1] which is still greatly under- and overdiagnosed as found in our study. Indeed, diagnostic difficulties have been stressed before, including the overlap in signs, symptoms, and risk factors, underuse of spirometry, and lower diagnostic accuracy of several tests,

including difficulties with interpreting spirometry results.[1, 10, 14, 16] This raises concerns regarding possible inappropriate treatment of COPD in an already vulnerable group of patients and as a result possible adverse impact on health and outcome.

Unfortunately, the current study was not large enough to find predictors of newly diagnosed COPD to make specific recommendations regarding which subgroup of patients should be tested. Also, it should be noted that a large proportion (69%) of newly diagnosed COPD patients according to GOLD criteria had only mild airway obstruction that may represent a physiological decline of lung function with age instead of a disease.[17, 18] It is unknown whether an additional diagnosis and treatment of COPD in these patients would improve health outcomes and change their prognosis. This warrants further research to establish the effectiveness of screening of patients with CHF for COPD in terms of symptomatic relief and improvement of the outcome as well as cost-effectiveness of such a policy. Until then, spirometry could be used in CHF patients with pulmonary symptoms despite an adequate treatment for their HF, especially in the presence of risk factors for COPD, such as a smoking history of ≥ 10 PY and occupational exposures. Importantly, spirometry should be used when clinically stable and euvolemic to avoid both misdiagnosis and inappropriate treatment of COPD.[1, 15] Under these conditions, a confirmatory spirometry seems to be unnecessary, as it did not change a newly established diagnosis of COPD in the vast majority of patients with CHF in our study (**chapter 2**). Finally, awareness of the co-occurrence of both diseases is essential among pulmonologists and cardiologists and collaboration between the two specialists is crucial to ensure optimal management of these patients. A better recognition and treatment of the two diseases may lead to less morbidity and mortality.

2. COPD in CHF: the LLN versus the fixed ratio of FEV_1/FVC

Spirometry is required for the diagnosis of COPD by measuring persistent airflow limitation.[19] However, there is still no consensus on the most appropriate threshold of FEV_1/FVC for diagnosing airflow limitation.[18, 20-29] The GOLD guidelines recommend the use of the fixed ratio of FEV_1/FVC < 0.70 for the sake of simplicity.[19] However, a growing body of literature indicates that considering the physiological decline of the FEV_1/FVC ratio with age the use of the fixed ratio may lead to overdiagnosis of COPD in elderly subjects[17, 30-45] and underdiagnosis of COPD in young adults.[38-47] To avoid misclassification, the ATS/ERS recommends the use of statistically derived LLN values for FEV_1/VC that are based on the normal distribution and that classify the bottom 5% of the healthy population as abnormal.[48] This is particularly important in patients with HF, given that HF is most prevalent among elderly individuals.[49] Thus, the earlier mentioned (**chapter 2**) and previously reported COPD prevalence rates (**chapter 1.3, Table 1**) based on the fixed ratio of 0.7 may have overestimated the true

prevalence of COPD in patients with HF. Although population-based studies have shown that the application of different criteria to define airflow obstruction dramatically changes the prevalence of COPD,[33-35, 50-53] it is less well understood to what extent this occurs in patients with HF.[54, 55] Therefore, the aim of the study presented in **chapter 3** was to determine COPD prevalence in patients with CHF according to two definitions of airflow obstruction: the LLN versus the fixed ratio of $FEV_1/FVC < 0.7$. We performed additional analysis in the same study population as described in **chapter 2**. The LLN was calculated by subtracting 1.64 times the RSD from the predicted value based on the reference values of the European Community for Coal and Steel.[56] We found that the exact definition of airflow obstruction altered COPD prevalence substantially; one fifth, rather than one third, of the patients with CHF had concomitant COPD using the LLN instead of the fixed ratio. This finding is in line with the results of Steinacher et al.[54] who reported COPD prevalence rates of 44% according to the GOLD criteria (fixed ratio) and 25% according to the ATS/ERS criteria (LLN) in 89 outpatients with stable CHF. However, this finding was not as well supported in another study of 118 elderly (≥ 65 years) patients with stable CHF, most likely because of the selection of patients with ≥ 10 PY (COPD prevalence 31% versus 29%).[55]

Thirty-eight percent of patients with GOLD-COPD in our study (**chapter 3**) were potentially misclassified as having COPD ($FEV_1/FVC < 0.7$ but > LLN). In contrast to patients with LLN-COPD, potentially misclassified patients did not differ significantly from those without COPD regarding respiratory symptoms and risk factors for COPD. LLN may therefore identify clinically more important COPD than the fixed ratio of 0.7.

An incorrect diagnosis of COPD may result in unnecessary treatment for COPD with possible side-effects and adverse cardiovascular events associated with pharmacological treatment for COPD and undertreatment with life-saving beta-blockers.[22, 57, 58] Moreover, an incorrect diagnosis and interventions for COPD may have a considerable psychological impact on the subject and his/her family and may lead to unnecessary costs.[22] Conversely, misclassifying a number of young adults already affected by COPD as healthy, prevents early interventions that could limit disease progression. Therefore, there is a need for clear diagnostic criteria for COPD to avoid diagnostic confusion, incorrect diagnosis, and inappropriate treatment.

Unfortunately, there is no gold standard for the diagnosis of COPD. The hallmark of the disease is the presence of airflow limitation that is not fully reversible and is usually progressive in nature.[19] However, there is no consensus on the spirometric criteria for the diagnosis of COPD.[18, 20-29] In theory, the most appropriate threshold for FEV_1/FVC in diagnosing COPD is the one with the best combination of sensitivity and specificity.[21] However, since there is no real gold standard for COPD calculating these numbers is

not possible and a true comparison of the fixed value and the LLN is not possible.[21] Considering the physiological decline of the FEV_1/FVC ratio with age, the application of statistically derived LLN values for FEV_1/FVC should be preferred to avoid overdiagnosis of COPD in elderly subjects[17, 30-45] and underdiagnosis in young adults.[38-47] However, when choosing appropriate cutoff values to define disease one should not only consider the statistical range of normality, but also clinically meaningful disease outcomes. An increasing number of studies have focused on the clinical impact of these different criteria. However, contrasting results have been reported and a recent review of 11 studies could not reveal a clear preference for one criterion over the other.[20] The results of some studies are in favor of using the fixed ratio of FEV_1/FVC < 0.7. Mannino et. al reported higher adjusted mortality risk[59, 60] and increased risk of COPD-related hospitalizations[59] in patients with FEV_1/FVC ratio < 0.7 but $>$ LLN ('in-between group') in comparison to subjects with normal lung function, suggesting that the fixed ratio of 0.7 identifies at-risk patients who would have been classified as normal according to the LLN. In addition, this in-between group has been reported to have a worse health-related quality of life than the non-COPD group in the study of García-Rio et.al.[32] However, no differences between the two groups were found in the same study for respiratory exacerbations, 6-minute walk distance, daily physical activity, systemic biomarkers, and cardiovascular disease, whereas patients with mild COPD did have more respiratory exacerbations, greater risk for cardiovascular disease, and greater serum concentrations of nitrites/nitrates than the control group.[32] Another cross-sectional study found this in-between group to have similar consumption of health-care resources (number of emergency room visits, hospitalizations due to COPD exacerbation, pharmacological treatment) and associated cardiovascular disorders, with exception of ischemic heart disease, compared to patients with LLN-COPD.[61] Furthermore, adopting an expert panel as the reference standard, the fixed ratio of FEV_1/FVC < 0.7 was more accurate to detect COPD in a symptomatic primary care population than the LLN.[62] Finally, subjects with airflow obstruction by fixed ratio only had a greater degree of emphysema, air wall thickening, and gas trapping using quantitative CT as gold standard than smoking controls without airflow obstruction.[63, 64] In addition, they had higher TLC, lower diffusing capacity, and more respiratory symptoms.[64] However, all of these variables were even more impaired in patients with airflow obstruction according to both the fixed ratio and the LLN.[63, 64] On follow-up, the fixed ratio only group had more exacerbations, higher scores on St. George's Respiratory Questionnaire, and more frequent initiation of oxygen therapy than smoking controls.[63]

The results of other studies are more in favor of using the LLN. Patients with FEV_1/FVC ratio < 0.7 but $>$ LLN did not show accelerated post-bronchodilator FEV_1 decline or more frequent exacerbations, whereas subjects with airway obstruction according to

the LLN did.[65, 66] Also, these patients did not seem to have clinically important airway obstruction in terms of the presence of respiratory symptoms, although they did report a diagnosis of heart disease more often than subject with normal lung function, suggesting that they might be at risk and should be followed carefully.[67] Additionally, the risk of death, COPD hospitalization, and the odds of having respiratory symptoms were only elevated amongst participants with FEV_1/FVC ratio < LLN.[68, 69] Furthermore, COPD according to the LLN criterion showed a stronger association with cardiac and all-cause hospitalization than COPD according to the fixed ratio.[70] Finally, misidentified subjects with lung function below the normal range (FEV_1/FVC ratio < LLN but > 0.7) had a significantly higher risk of developing COPD and a higher use of health resources because of breathing problems than subjects without airflow obstruction.[46, 71]

The results of Wollmer et. al did not favor either the LLN or the fixed ratio, but found the group of patients with FEV_1/FVC ratio < 0.7 but > LLN to form an intermediate group with respect to lung function impairment and mortality rates,[72] implicating that careful evaluation of patient history and extended PFTs may be warranted in this group of patients. More longitudinal studies are needed to determine which criterion is better and clinically more relevant.[20, 21]

In clinical practice, decisions are not made on the basis of a single test and there are diagnostic difficulties that go beyond the discussion regarding which definition should be used. It is not possible to categorically separate sick from healthy individuals based on spirometry, since there is some overlap in FEV_1/FVC ratio between those with and without respiratory disease, independent of the definition used. Therefore, there is always the risk of false positive and false negative results, especially in the grey area between normal and abnormal pulmonary function. Moreover, both definitions cannot exclude airflow obstruction with certainty because, in a minority of cases, FEV_1 and FVC may be decreased proportionally as a result of an isolated increase in RV,[48] which may lead to a false diagnosis of restriction instead of obstruction. Also, conditions that increase lung stiffness, such as interstitial edema in HF, may mask airflow obstruction.[73]Additional body plethysmography may therefore be necessary for the correct diagnosis. Furthermore, reduced FEV_1/FVC ratio with normal FEV_1 may represent a physiological variant possibly due to dysanaptic lung growth, by which lung volume is disproportionately large compared with airway size.[73] Finally, structural lung changes (emphysema) may already be present before or even in the absence of airflow limitation.[73] In light of these diagnostic difficulties, a more comprehensive approach is required, taking into account clinical features, pulmonary function tests, and radiological findings. Clinical findings, including history and exposure to risk factors, can facilitate the diagnosis of COPD,[19] and the physician ultimately determines the medical significance of an abnormal spirometric value

based on these clinical findings. In support, an expert diagnosis of COPD has been found to better predict COPD exacerbations, hospitalizations, and mortality than GOLD or LLN criteria.[74] However, these decisions are more complicated in patients with HF due to overlap in signs and symptoms as well as risk factors.[1] Extended PFTs, including diffusion capacity and body plethysmography, may be warranted to facilitate correct diagnosis in this group of patients. Indeed, from all PFT variables (besides FEV_1/FVC), FEV_1, RV/TLC, and diffusing capacity performed best in predicting an expert diagnosis of COPD.[74] Moreover, incorporating FEV_1 and RV/TLC into the GOLD-COPD and LLN-based definition improved the diagnostic accuracy significantly and brought both definitions closer to expert panel diagnosis of COPD and to daily clinical practice.[74] Finally, radiological findings (computed tomography) may advance further decision making.

3 Pulmonary function impairment in CHF

Isolated or combined pulmonary function abnormalities, such as restriction, diffusion impairment, and to a lesser extent airway obstruction are common in patients with CHF[75-82] and can contribute to the perception of dyspnea[83] and exercise intolerance.[83-89] Reported prevalence rates of pulmonary function abnormalities in patients with CHF vary substantially between 41% and 93% for diffusion impairment, 21-55% for restriction, and 14-60% for airway obstruction (**chapter 1.4, Table 2)**. These varying rates across the studies can be partly explained by the usually small number of patients included and differences in study population as well as diagnostic criteria used to define pulmonary function abnormalities. The majority of studies have used conventional cutoff values to define an abnormality, failing to diagnose pulmonary function impairment according to internationally accepted diagnostic criteria.[48] These conventional cutoff values have neither statistical nor physiological validity[48, 90] and may misclassify more than 20% of patients leading to false-positive diagnosis in the elderly and underdiagnosis in younger patients.[38] Therefore, pulmonary function abnormalities may have been overestimated in previous studies of mainly old CHF patients. Moreover, some studies described a restrictive lung function defect on the basis of reduced FEV_1 and FVC with normal FEV_1/FVC ratio.[91] However, because FEV_1 and FVC may also be proportionately reduced with a normal ratio in patients with severe COPD and gas trapping, the diagnosis of restriction additionally requires detection of reduced TLC by plethysmography. Finally, a large number of studies have included (potential) heart transplant recipients, who represent one extreme of the HF spectrum.[91-97] Therefore, it is less known to what extent CHF patients who do not belong to the most severe category of HF have pulmonary function abnormalities and which of these abnormalities prevail. Given the gaps in current knowledge we investigated the occurrence of pulmonary function abnormalities in 164 outpatients with CHF with LVSD according to the LLN versus conventional cutoff values (i.e.

FEV_1/VC < LLN versus FEV_1/FVC < 0.7 for airway obstruction, TLCOc < LLN versus < 80% predicted for diffusion impairment, and TLC < LLN versus < 80% predicted for restriction) **(chapter 4)**. We excluded patients with known pulmonary, pleural (with exception of pleural effusion due to HF), neuromuscular, collagen vascular, or other diseases that could affect pulmonary function. Patients with a BMI above 35 were excluded from the restriction prevalence analysis. Pulmonary function abnormalities, especially diffusion impairment and airway obstruction, were found to be highly prevalent in patients with CHF, even in a stable and non-congested condition and even though we used the LLN to better account for age. However, prevalence rates varied significantly according to the definition used between 44% and 58% for diffusion impairment and between 26% and 37% for airway obstruction using the LLN versus conventional cutoff values, respectively. In contrast to previous reports, restriction was found to be infrequent in this population of less severe and mainly stable CHF patients without pulmonary congestion, irrespective of the definition used (7% versus 5%, respectively). The conventional cutoff values classified more patients as having diffusion impairment, airway obstruction, or a mixed category compared to the LLN and failed to identify correctly 34% of patients with normal lung function placing them falsely within a pulmonary dysfunction category. Using the conventional cutoff values instead of the LLN led to misclassification of 27% of the patients.

Misinterpretation of pulmonary function test results may lead to incorrect diagnosis of disease in elderly patients with HF, such as COPD, and as a consequence unnecessary treatment with possible side effects, detrimental psychological impact, and needless costs. Moreover, results may be interpreted as having more severe or unstable HF due to the effects of HF on pulmonary function and as a result unnecessary intensified treatment for HF. Finally, misdiagnosis may have interfered with the interpretation of prior research aiming to investigate the impact of HF and several clinical variables on pulmonary function. Therefore, the purpose of the study presented in **chapter 5** was to assess predictors of pulmonary function impairment in 164 outpatients with CHF with LVSD according to the LLN in comparison to conventional cutoff values (percent predicted and the fixed ratio of FEV_1/FVC). The same exclusion criteria as described in **chapter 4** were applied. We found that the LLN criterion identified an extra independent predictor of diffusion impairment compared to the 80% predicted value; in addition to BMI, PY, and VA, female gender also turned out to be an independent predictor of diffusion impairment using the LLN. Furthermore, a smoking history of ≥ 10 PY was a significant predictor of diffusion impairment and airway obstruction using the LLN criterion, but not using the conventional cutoff values, implying that inclusion of patients who are incorrectly labeled as having pulmonary dysfunction distorted the effect of smoking on pulmonary function. Lowering the cutoff points of conventional criteria to match the

more stringent LLN and thus avoid overdiagnosis of diffusion impairment and airway obstruction in the elderly, produced similar results as the LLN. Finally, lower lung volumes were found in patients with pulmonary congestion, cardiomegaly, and a history of CABG.

Several factors have been implied to play a role in the etiology of pulmonary function impairment in patients with HF, including the effects of HF itself on pulmonary function in addition to confounding influences such as smoking, CABG, and obesity.[75-82, 98, 99] Physicians should also consider the possibility that pulmonary function impairment in patients with HF represents previously undiagnosed pulmonary disease such as COPD. In fact, COPD is frequently unrecognized in patients with HF (**chapter 1.3, Table 1**). A careful evaluation of the patient and potential treatment options is therefore necessary before ascribing pulmonary function impairment only to the effects of HF.

Although the underlying mechanisms are not clear, women seemed to be more sensitive to the detrimental effects of HF on diffusing capacity in our study. Gender differences in pulmonary function have been recognized before, but not specifically in the HF population. Adult women have been reported to have lower resting lung diffusing capacity corrected for hemoglobin, smaller lung volumes, and lower maximal expiratory flow rates, even when corrected for age and standing height relative to men.[100] It has been suggested that these gender differences in part can be explained by pulmonary structural differences (fewer total number of alveoli and smaller airway diameter relative to lung size) and hormonal influences in women.[100] More research is needed regarding the influence of gender on pulmonary function in general and specifically in the HF population.

The protective association between a higher BMI and less likelihood of having diffusion impairment has not been described before in patients with CHF. However, some studies in healthy obese nonsmokers have suggested that diffusing capacity may be increased in extremely obese subjects, probably as a result of the increase in blood volume.[101]

Irrespective of the causes, pulmonary function abnormalities associated with CHF may explain part of the symptoms and functional disability encountered in these patients.[83-89, 102] Moreover, pulmonary function impairment increases with the severity of HF,[87, 88, 103] provides important prognostic information,[104-107] and may ameliorate or normalize with several treatment modalities, such as pharmacological and non-pharmacological treatment of HF and anti-obstructive therapy with bronchodilators as described in the general introduction. Pulmonary function might thus be used as a guide for the evaluation of patients with CHF, with respect to severity of disease,

prognosis, and response to treatment. More studies involving therapeutic approaches to improve pulmonary function in CHF are warranted to determine whether treatment directed at correcting pulmonary function impairment may lead to symptomatic relief, increased exercise capacity, and improvement of the outcome.

4. The role of inhaled bronchodilators in CHF

As mentioned before, airway obstruction may be present in patients with CHF. Treatment directed at reversing airway obstruction with bronchodilators may thus have an additional role in the management of HF. There are, however, only few studies concerning the beneficial effects of bronchodilators in patients with HF. Improvements in pulmonary function,[108-114] dyspnea,[111] and exercise performance[114] have been reported. Some investigators have even observed an increase of mean FEV_1 greater than 200 mL and 12% in patients with HF,[108-110] especially in those with airway obstruction,[109] LVSD,[108] and during acute decompensation of HF.[110] However, not all could confirm these findings.[111, 114-118] Contrasting results across the studies might be attributed to the small number of patients studied and to the differences in study population, bronchodilators used, and definition of BDR. The purpose of the retrospective observational study presented in **chapter 6** was to evaluate the effect of maximal bronchodilation with combined inhaled salbutamol (400 μg) and ipratropium bromide (80 μg) on pulmonary function and dyspnea in 116 patients with CHF without a history of COPD or asthma. In addition, we determined the proportion of patients with significant BDR (i.e. responder), defined as post-bronchodilator increase in FEV_1 greater than 200 mL and 12% from the baseline value. Since there is no consensus about the drug, dose, or mode of administering a bronchodilator to test BDR,[48] and BDR may differ with the bronchodilator used, we sought to obtain maximal bronchodilation by combining two bronchodilators with different mechanisms of action. The results of our study confirmed that inhaled bronchodilators have the potential to improve pulmonary function in patients with CHF, especially in those with airway obstruction. Importantly, full reversal of airway obstruction was seen in approximately 40% of patients without a history of COPD or asthma who had pre-bronchodilator airway obstruction. Significant improvements in pulmonary function were noted in all spirometric indices except for FVC and IC in the entire study population. Significant BDR of FEV_1 was noted in 12%. Patients with persisting airway obstruction and those with fully reversible airway obstruction had significant BDR of FEV_1 more often than patients without airway obstruction (23%, 16%, and 2%, respectively). Improvement in dyspnea at rest after bronchodilation was, however, small and did not correlate to improvement in pulmonary function.

The bronchodilatory effect is most probably explained by a reduction in the increased bronchial tone which may contribute to airway obstruction in patients with HF. Also,

acutely delivered beta-agonists may act by improving cardiovascular hemodynamics and resorption of pulmonary edema.[119] However, considering the speed with which bronchodilation took place and the fact that most patients were not congested on chest radiograph, this was likely not the main mechanism of action. Also, we observed an increase in mean FEV_1 and a decrease in mean FVC in the fully reversible group of patients, while the group with persistent airway obstruction did in fact show an increase in both parameters. This may explain why the group with persistent airway obstruction maintained a low ratio of FEV_1/FVC after bronchodilation while this ratio normalized in the group with reversible airway obstruction. Finally, we cannot exclude the possibility that some of the patients with complete reversal of airway obstruction in our study may have had previously undiagnosed asthma, as new-onset asthma may occur at any age and is often underrecognised or misdiagnosed in the elderly.[120] However, there was no indication of asthma based on symptoms and physical examination in these patients except for one patient who was diagnosed with asthma after having participated in our study. Excluding this patient from the analysis still yielded similar rates of fully reversible airway obstruction (38%).

The incomplete reversal of airway obstruction in other patients may be due to irreversible anatomical alterations of the bronchial wall or subclinical pulmonary congestion. In addition, previously undiagnosed pulmonary disease, such as COPD, bronchiectases, and late-onset asthma, should also be considered in the differential diagnosis of fixed airway obstruction.

Another interesting finding of our study was that the use of non-selective beta-blockers instead of selective beta-blockers resulted in less reversibility of IC and FEF_{50}. This finding is in line with prior evidence that non-selective beta-blockers may antagonize beta-agonists.[57] In contrast, baseline pulmonary function, the prevalence of airway obstruction, and improvement of dyspnea were not affected by the type of beta-blocker used.

Although post-bronchodilator improvements in resting dyspnea were clinically small and not related to improvements in pulmonary function in this selected study population, greater symptomatic relief might be possible in more symptomatic patients and with longer duration of treatment. Further RCTs are needed to examine the clinical benefits as well as potential adverse events of bronchodilators in the treatment of CHF.[121] Concerns have been raised regarding the cardiovascular safety profile of these drugs.[57, 121-124] Recently, reassuring cardiovascular safety data have been reported on long-acting anticholinergic bronchodilator tiotropium HandiHaler[125-133] as well as Respimat.[134] However, HF patients are usually excluded from clinical trials and the impact of bronchodilators on outcomes has never been prospectively evaluated in

patients with HF.[121] Furthermore, methodological limitations of most studies require further investigation of reported adverse events.[57, 121] Until then, bronchodilators, in particular beta-agonists, must be used with caution in patients with underlying cardiac condition such as HF, given the paucity of data in such patients.

Future perspectives

Although this thesis has provided answers to many questions, there are still many challenges for future research.

Despite the close relationship between lung and heart diseases, pulmonologists and cardiologists often focus on their own field of specialization.[8] Meanwhile, HF and COPD often remain an ignored combination[11] and the degree of awareness is low among both cardiologists as well as pulmonologists.[135] In view of diagnostic, therapeutic, and prognostic implications of the coexistence of COPD and HF, more attention should be paid to the concomitant presence of both diseases in clinical practice and research.[11] A more combined and integrated approach in the diagnosis and treatment of concurrent COPD and HF is required.

Although we found COPD to be frequently unrecognized in patients with CHF (**chapter 2** and **3**), it is unknown whether an additional diagnosis and treatment of COPD in these patients will improve health outcomes and change their prognosis. This warrants further research to establish the effectiveness of screening of patients with CHF for COPD in terms of symptomatic relief and improvement of the outcome as well as cost-effectiveness of such a policy. Additionally, future research should focus on the cardiovascular safety profile of bronchodilators, especially in patients with underlying cardiac condition such as HF.

Furthermore, our findings stress the need for a clear definition of COPD, especially in patients with HF in whom the diagnosis of COPD is already complicated and who are prone to the adverse effects of pharmacological treatment for COPD. Considering the ongoing debate regarding the most appropriate threshold for FEV_1/FVC in diagnosing COPD, more longitudinal studies are needed to determine which criterion is better and clinically more relevant in terms of morbidity (symptoms, exercise tolerance, health-related quality of life, exacerbations, hospitalization, pulmonary function decline, use of health recourses, systemic effects such as co-morbidities and systemic biomarkers) and mortality. The question is whether patients potentially misclassified as having COPD ($FEV_1/FVC < 0.7$ but $>$ LLN) actually show clinical features that justify a COPD diagnosis or whether they behave more like a healthy population. Until a consensus is reached, we prefer the application of statistically derived LLN values to avoid overdiagnosis of COPD in the elderly and underdiagnosis in younger patients, and advocate a more comprehensive approach, taking into account clinical features, the results of extended PFTs, and radiological findings.

Similarly, little is known about the clinical impact of different criteria of pulmonary dysfunction and this therefore requires more longitudinal research. Although we found pulmonary function abnormalities to be highly prevalent in patients with CHF, it remains unknown, due to lack of follow-up, whether pulmonary function impairment had prognostic implications in our study population and whether this has been influenced by different definitions of pulmonary dysfunction. Also, more studies involving therapeutic approaches to improve pulmonary function in CHF are warranted to determine whether treatment directed at correcting pulmonary function impairment may lead to symptomatic relief, increased exercise capacity, and improvement of the outcome. The clinical usefulness and possible adverse events of bronchodilators need to be further established. The results of our retrospective observational study regarding the effects of inhaled bronchodilators on pulmonary function and dyspnea in patients with CHF (**chapter 6**) should be confirmed in large RCTs in both stable and decompensated conditions of HF and short-term as well as long-term treatment and follow-up. Moreover, the effects of salbutamol and ipratropium should also be studied separately. In addition, the effects of bronchodilators on other outcomes should be investigated, including quality of life, exercise performance, airway resistance, hospitalization, and survival. Furthermore, whether the presence or absence of significant BDR in patients with CHF predicts prognostic outcome and clinical response to bronchodilators has not been investigated before and needs further research. The small improvement in dyspnea after bronchodilation was not significantly different between responders or non-responders in our patients with CHF.

Although the underlying mechanisms are not clear, women seemed to be more sensitive to the detrimental effects of HF on diffusing capacity. This needs to be confirmed and further explored in future studies.

Finally, since we only included patients with HF-REF, our results cannot be extended to patients with HF-PEF and more research is warranted in this group of patients.

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CHAPTER 8

Samenvatting

Conclusies

Toekomstperspectief

Samenvatting

Het doel van dit proefschrift is het verschaffen van meer inzicht in het vóórkomen van chronisch obstructieve longziekte (COPD) en longfunctiestoornissen, gebruikmakende van verschillende definities, bij patiënten met chronisch hartfalen (CHF). Daarnaast was ons streven om onder- en overdiagnostiek van COPD in kaart te brengen en de noodzaak te bepalen van het herhalen van longfunctietesten om een correcte diagnose van COPD te stellen. Tevens wilden wij mogelijke voorspellers van longfunctiestoornissen bij patiënten met CHF identificeren. Wederom hebben wij hiervoor gebruikgemaakt van verschillende definities van longfunctiestoornissen. Tenslotte wilden wij het effect van luchtwegverwijdende medicijnen bepalen op de longfunctie en kortademigheid bij patiënten met CHF.

In **hoofdstuk 2** bepaalden wij het vóórkomen van COPD alsook de over- en onderdiagnostiek hiervan volgens de veel gebruikte GOLD definitie bij 187 poliklinische patiënten met stabiel CHF. Alle patiënten hadden een verminderde pompfunctie van de linker hartkamer zonder aanwijzingen voor longvaatovervulling. Daarnaast onderzochten wij of het nodig is om longfunctietesten te herhalen om daarmee een correcte diagnose van COPD te kunnen stellen. Hiertoe maakten wij gebruik van een initiële alsook een vervolgspirometrie drie maanden na behandeling met tiotropium, een luchtwegverwijdend medicijn, bij patiënten met een nieuw gestelde COPD diagnose. COPD kwam vaak voor bij patiënten met CHF; het werd gevonden bij ongeveer eenderde van de patiënten. Bovendien bleek COPD vaak onder- (19%) of juist overgediagnosticeerd (32%) te zijn. Wij concludeerden dat onder stabiele en niet-overvulde omstandigheden het niet noodzakelijk is om spirometrie te herhalen voor het stellen van een correcte diagnose van COPD, aangezien een nieuw gestelde COPD diagnose gehandhaafd bleef bij de meerderheid van de patiënten met CHF.

In **hoofdstuk 3** bepaalden wij het vóórkomen van COPD in dezelfde studiepopulatie als beschreven in hoofdstuk 2, waarbij we twee definities van luchtwegvernauwing vergeleken: de 'lower limit of normal' (LLN) (ATS/ERS richtlijn) en de vaste afkapwaarde van het geforceerde expiratoire volume in één seconde ten opzichte van de geforceerde vitale capaciteit (FEV_1/FVC) < 0.7 (GOLD richtlijn). Wij vonden dat COPD substantieel minder vaak voorkwam volgens de LLN dan volgens de vaste afkapwaarde; slechts één op de vijf, in plaats van één op de drie, patiënten met CHF bleek tevens COPD te hebben. Bovendien bleken patiënten met COPD volgens de LLN definitie klinisch meer relevant COPD te hebben dan patiënten met COPD volgens de conventionele afkapwaarde. Achtendertig procent van de patiënten met GOLD-COPD die mogelijk onterecht bestempeld waren als COPD patiënt (FEV_1/FVC < 0.7 maar $>$ LLN) verschilden namelijk niet significant van degenen zonder COPD

in termen van longklachten en risicofactoren voor COPD, dit in tegenstelling tot patiënten met LLN-COPD.

In **hoofdstuk 4** onderzochten wij het vóórkomen van longfunctiestoornissen bij 164 poliklinische CHF patiënten met een verminderde pompfunctie van de linker hartkamer. Hiertoe hebben wij gebruikgemaakt van de LLN versus de conventionele afkapwaarden, oftewel $FEV_1/VC < LLN$ versus $FEV_1/FVC < 0.7$ voor het definiëren van luchtwegvernauwing, diffusiecapaciteit < LLN versus < 80% van voorspeld voor het definiëren van verminderde zuurstofopname en totale longcapaciteit < LLN versus < 80% van voorspeld voor het definiëren van een kleine longinhoud. Wij sloten patiënten uit met bekende aandoeningen aan long, longvlies, zenuw- en spierstelsel, bindweefsel en vaten, of andere aandoeningen die de longfunctie konden beïnvloeden. Patiënten met een 'body mass index' (BMI) boven de 35 werden uitgesloten van de analyse naar het vóórkomen van een kleine longinhoud. Longfunctiestoornissen, met name verminderde zuurstofopname en luchtwegvernauwing, kwamen vaak voor bij patiënten met CHF. Dit was zelfs het geval gedurende een stabiele en niet-overvulde klinische toestand en ondanks het gebruik van de LLN om rekening te houden met de gevorderde leeftijd van de patiënten. Echter, zowel een verminderde zuurstof- opname alsook luchtwegvernauwing kwamen significant minder vaak voor volgens de LLN dan wanneer we gebruikmaakten van de conventionele afkapwaarden: respectievelijk 44% versus 58% en 26% versus 37%. In tegenstelling tot eerdere studies werd een kleine longinhoud weinig waargenomen, onafhankelijk van de gebruikte definitie, in deze populatie van minder ernstig aangedane en hoofdzakelijk stabiele CHF patiënten zonder longvaatovervulling (respectievelijk 7% en 5%). De conventionele afkapwaarden classificeerden meer patiënten tot het hebben van een verminderde zuurstofopname, luchtwegvernauwing, of gecombineerde longfunctiestoornis in vergelijking met de LLN. Daarbij waren ze nalatig in het correct identificeren van 34% van de patiënten met een normale longfunctie, waardoor deze onterecht in de groep met longfunctiestoornissen geclassificeerd werden. Het gebruik van de conventionele afkapwaarden in plaats van de LLN leidde tot misclassificatie van 27% van de patiënten.

In **hoofdstuk 5** onderzochten wij voorspellers van longfunctiestoornissen volgens de LLN in vergelijking met de conventionele afkapwaarden bij 164 poliklinische CHF patiënten met een verminderde pompfunctie van de linker hartkamer. Dezelfde uitsluitingscriteria als beschreven in hoofdstuk 4 werden gebruikt. De LLN identificeerde een extra onafhankelijke voorspeller van verminderde zuurstofopname in vergelijking met de 80% voorspelde waarde; naast de BMI, het aantal gerookte pakjaren en het longvolume, bleek het vrouwelijk geslacht ook een onafhankelijke voorspeller te zijn van verminderde zuurstofopname op basis van de LLN. Het roken van ≥ 10 pakjaren

was een significante voorspeller van zowel verminderde zuurstofopname als luchtwegvernauwing gebruikmakende van de LLN, maar niet volgens de conventionele afkapwaarden. Echter, door het verlagen van de conventionele afkapwaarden om de meer strenge LLN te evenaren en hiermee overdiagnostiek van verminderde zuurstofopname en luchtwegvernauwing bij ouderen te voorkomen, werden vergelijkbare resultaten verkregen als met de LLN. Lagere longvolumina werden gevonden bij patiënten met longvaatovervulling, hartvergroting, en een voorgeschiedenis van bypassoperatie aan de kransslagaders.

Tenslotte evalueerden wij in **hoofdstuk 6** retrospectief het effect van luchtwegverwijdende medicijnen (gecombineerd 400 μg salbutamol en 80 μg ipratropium bromide) op de longfunctie en kortademigheid bij 116 poliklinische CHF patiënten met verminderde pompfunctie van de linker hartkamer. Patiënten met een voorgeschiedenis van COPD of astma werden uitgesloten. De resultaten van onze studie bevestigden dat luchtwegverwijdende medicijnen het vermogen hebben om de longfunctie bij patiënten met CHF te verbeteren, voornamelijk bij degenen met een luchtwegvernauwing. Bij ongeveer 40% van de patiënten met luchtwegvernauwing zonder bekend COPD of astma trad een volledig herstel op van de longfunctie na toediening van luchtwegverwijdende medicijnen. Alle longfunctionele waarden verbeterden significant in de gehele studiepopulatie, met uitzondering van de FVC en de inspiratoire capaciteit. Bij 12% werd een aanzienlijke verbetering van de FEV_1 waargenomen (> 200 mL en > 12% van de uitgangswaarde) na toediening van luchtwegverwijdende medicijnen. Patiënten met luchtwegvernauwing, zowel degenen met als zonder volledig herstel na toediening van luchtwegverwijdende medicijnen, vertoonden vaker een aanzienlijke verbetering in FEV_1 dan patiënten zonder luchtwegvernauwing (respectievelijk 23%, 16% en 2%). Verbetering van kortademigheid in rust na luchtwegverwijding was daarentegen klein en bleek niet gecorreleerd te zijn met de verbeteringen in longfunctie in deze geselecteerde studiepopulatie.

Conclusies

- COPD is een veelvoorkomende aandoening bij patiënten met stabiel CHF die een verminderde pompfunctie van de linker hartkamer hebben zonder aanwijzingen voor longvaatovervulling. COPD wordt echter vaak onder- of juist overgediagnosticeerd.

- Spirometrie dient gebruikt te worden tijdens een stabiele en gerecompenseerde klinische toestand om de hoge mate van onderdiagnostiek danwel overdiagnostiek van COPD te verminderen bij patiënten met CHF. Onder deze omstandigheden is het niet noodzakelijk om spirometrie te herhalen ter bevestiging van de diagnose COPD, aangezien dit een nieuw gestelde COPD diagnose niet verandert bij de overgrote meerderheid van de patiënten met CHF.

- De gebruikte definitie van luchtwegvernauwing verandert de mate van voorkomen van COPD substantieel; eenvijfde, in plaats van eenderde, van de patiënten met CHF heeft tevens COPD gebruikmakende van de LLN in plaats van de vaste afkapwaarde.

- De LLN definitie lijkt patiënten te identificeren met klinisch meer relevant COPD dan de vaste afkapwaarde van 0.7. Dit vloeit voort uit de bevinding dat patiënten die potentieel onterecht bestempeld zijn als COPD patiënt, in tegenstelling tot degenen met LLN-COPD, niet significant verschillen van degenen zonder COPD in termen van longklachten en risicofactoren voor COPD.

- Longfunctiestoornissen, met name verminderde zuurstofopname en luchtwegvernauwing, zijn veelvoorkomend bij patiënten met CHF.

- De conventionele afkapwaarden classificeren meer patiënten tot het hebben van een verminderde zuurstofopname, luchtwegvernauwing danwel gecombineerde longfunctiestoornis in vergelijking met de LLN, hetgeen leidt tot misclassificatie van 27% van de patiënten.

- De LLN identificeert meer voorspellers van verminderde zuurstofopname en luchtwegvernauwing dan de conventionele afkapwaarden. Echter, lagere conventionele afkapwaarden resulteren in vergelijkbare uitkomsten als de strengere LLN.

- Luchtwegverwijdende medicijnen zijn mogelijk van toegevoegde waarde bij de behandeling van patiënten met CHF in verband met hun vermogen om de longfunctie te verbeteren, voornamelijk bij degenen met luchtwegvernauwing. Verbetering van kortademigheid daarentegen is klein en niet gecorreleerd met de verbeteringen in longfunctie in deze geselecterde studiepopulatie.

Toekomstperspectief

Hoewel dit proefschrift vele vragen heeft beantwoord, zijn er nog meer dan genoeg uitdagingen voor toekomstige studies.

Ondanks de nauwe relatie tussen long- en hartaandoeningen richten longartsen en hartspecialisten zich vaak teveel op hun eigen vakgebied.[1] Ondertussen blijven hartfalen en COPD dikwijls een onderschatte combinatie[2] en de mate van besef hiervan is laag onder zowel hartspecialisten als longartsen.[3] Aangezien het gezamenlijk voorkomen van COPD en hartfalen gevolgen kan hebben voor diagnostiek, behandeling en prognose van deze patiëntengroep, is zowel meer aandacht in de kliniek vereist als meer onderzoek naar de gelijktijdige aanwezigheid van beide ziektes.[2] Een meer gecombineerde en geïntegreerde aanpak van diagnostiek en behandeling van COPD en hartfalen is noodzakelijk.

Hoewel COPD dikwijls onderschat blijkt te zijn bij patiënten met CHF (**hoofdstuk 2** en **3**), is het onbekend of een additionele diagnose en behandeling van COPD in deze patiëntenpopulatie hun gezondheidsuitkomsten zal verbeteren en de prognose zal veranderen. Dit behoeft verder onderzoek om de effectiviteit van het screenen van patiënten met CHF op COPD te bepalen in termen van symptoomverlichting en verbetering van de gezondheidsuitkomsten alsook de kosteneffectiviteit van een dergelijke aanpak. Daarnaast dient toekomstig onderzoek zich te richten op de cardiovasculaire veiligheid van luchtwegverwijdende medicijnen, voornamelijk bij patiënten met een onderliggende hartziekte als hartfalen.

Voorts benadrukken onze bevindingen de noodzaak van een duidelijke definitie van COPD, in het bijzonder bij patiënten met hartfalen bij wie de diagnose van COPD reeds bemoeilijkt is en die gevoelig zijn voor de bijwerkingen van medicamenteuze behandeling van COPD. Gezien de lopende discussie omtrent de meest geschikte afkapwaarde voor FEV_1/FVC om de diagnose COPD te stellen, zijn meer lange-termijn studies nodig om te bepalen welke definitie beter en klinisch meer relevant is in termen van mortaliteit en ziektelast (symptomen, inspanningstolerantie, gezondheidsgerelateerde kwaliteit van leven, opvlamming van ziekte, ziekenhuisopnames, achteruitgang van de longfunctie, gebruik van gezondheidszorg, systemische effecten zoals het tegelijk voorkomen van meerdere ziektes en systemische biomarkers). De hamvraag is of patiënten die mogelijk onterecht bestempeld zijn als COPD patiënt ($FEV_1/FVC < 0.7$ maar $>$ LLN) daadwerkelijk klinische kenmerken vertonen die een diagnose van COPD rechtvaardigen of dat ze toch meer gelijkenis vertonen met de gezonde populatie. Totdat consensus is bereikt, geven wij de voorkeur aan het gebruik van statistisch afgeleide LLN om overdiagnostiek van

COPD te vermijden bij de ouderen en onderdiagnostiek bij de jongere patiënten. Tevens pleiten wij voor een meer uitgebreide aanpak, rekening houdende met klinische kenmerken, resultaten van uitgebreidere longfunctietesten en radiologische bevindingen.

Evenzo is er slechts weinig bekend over de klinische relevantie van verschillende definities van longfunctiestoornissen en is dan ook meer longitudinaal onderzoek vereist. Ondanks onze bevinding dat longfunctiestoornissen veelvoorkomend zijn bij patiënten met CHF, blijft het zonder follow-up onbekend of de aanwezigheid van longfunctiestoornissen prognostische gevolgen had in onze studiepopulatie en of dit beïnvloed werd door het gebruik van verschillende definities voor longfunctiestoornissen. Tevens zijn meer studies nodig gericht op de vraag of behandeling van longfunctiestoornissen bij hartfalen leidt tot symptoomverlichting, toegenomen inspanningstolerantie en verbetering van de uitkomsten. De klinische toepasbaarheid en mogelijke bijwerkingen van luchtwegverwijdende medicijnen dienen verder te worden onderzocht. De resultaten van onze retrospectieve observationele studie betreffende de effecten van luchtwegverwijdende medicijnen op de longfunctie en kortademigheid bij patiënten met CHF (**hoofdstuk 6**) dienen te worden bevestigd in grote gerandomiseerde en gecontroleerde studies met zowel stabiele als gedecompenseerde hartfalen patiënten alsook kortdurende en langdurige behandeling en follow-up. Bovendien dienen de effecten van salbutamol en ipratropium ook apart te worden onderzocht. Daarnaast dienen de effecten van luchtwegverwijdende medicijnen op andere uitkomstparameters te worden onderzocht, zoals kwaliteit van leven, inspanningstolerantie, luchtwegweerstand, ziekenhuis opnames en overleving. Tevens is het onbekend of de aan- of afwezigheid van significante verbetering van de longfunctie bij patiënten met CHF voorspellend is voor hun prognose en klinische respons op luchtwegverwijdende medicatie. Dit behoeft dan ook verder onderzoek. De kleine verbetering in kortademigheid na luchtwegverwijdende medicijnen was niet significant verschillend bij onze CHF patiënten met of zonder significante verbetering van de longfunctie.

Ofschoon de onderliggende mechanismen vooralsnog onbekend zijn, bleken vrouwen meer vatbaar te zijn voor de nadelige gevolgen van hartfalen op zuurstofopname. Dit dient te worden bevestigd en verder toegelicht in toekomstige studies.

Tenslotte, aangezien we enkel hartfalen patiënten met een verminderde pompfunctie hebben onderzocht, zijn onze resultaten niet toepasbaar op hartfalen patiënten met een behouden pompfunctie. Meer onderzoek is nodig in deze patiëntengroep.

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CHAPTER 9

List of publications

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Minasian AG, van den Elshout FJ, Dekhuijzen PN, Vos PJ, Willems FF, van den Bergh PJ, Heijdra YF. Serial pulmonary function tests to diagnose COPD in chronic heart failure. Translational Respiratory Medicine. 2014;2:12.

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List of abbreviations

A	Age
ABHR	Aspecific bronchial hyperreactivity
ACE-I	Angiotensin-converting enzyme inhibitor
AF	Atrial fibrillation
AO	Airway obstruction
ARB	Angiotensin receptor blocker
ATS/ERS	American Thoracic Society/European Respiratory Society
BB	Beta-blockers
BDR	Bronchodilator responsiveness
BMI	Body mass index
BNP	B-type natriuretic peptide
BOLD	Burden of Obstructive Lung Disease
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Chronic heart failure
CMP	Cardiomyopathy
CoHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CRT	Cardiac resynchronization therapy
CS	Current smokers
CTR	Cardiothoracic ratio
D	Diffusion impairment
DLCO(c)	Diffusion capacity of the lung for carbon monoxide (corrected for hemoglobin concentration)
ECCS	European Community for Coal and Steel
ESC	European Society of Cardiology
FEF_{50}	Forced expiratory flow at 50% of forced vital capacity
FEF_{25-75}	Forced expiratory flow at 25-75% of forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FEV_1/FVC	Ratio of forced expiratory volume in 1 second to forced vital capacity
FRC	Functional residual capacity (= ITGV)
FS	Former smokers
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
H	Height
HF	Heart failure
HF-PEF	Heart failure with preserved ejection fraction
HF-REF	Heart failure with reduced ejection fraction
IC	Inspiratory capacity
ICD	Implantable cardioverter defibrillator
ICS/OCS	Inhalation/oral corticosteroids
ITGV	Intra-thoracic gas volume (= FRC)
KCO(c)	Transfer coefficient for carbon monoxide (corrected for hemoglobin concentration) = TLCO(c)/VA
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
M	Months
MLHFQ	Minnesota Living with Heart Failure Questionnaire

MRC	Modified Medical Research Council dyspnea scale
NA	Not available
NHANES	National Health and Nutrition Examination Survey
No.	Number of patients
NS	Non-smokers
NT-pro-BNP	N-terminal pro-B natriuretic peptide
NYHA	New York Heart Association
O	Airway obstruction
OLD	Obstructive lung disease
P	Prospective
PAP	Pulmonary artery pressure
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PEF	Peak expiratory flow
PEEP	Positive end-expiratory pressure
PFTs	Pulmonary function tests
Pre-/post-BD	Pre/post-bronchodilator
% Pred.	Percent predicted
PY	Pack-years
R	Restriction; retrospective (Table 1)
Raw	Airway resistance
RCT	Randomized controlled trial
RSD	Residual standard deviation
RV	Residual volume
SD	Standard deviation
SE(E)	Standard error (of the estimate)
sGaw	Specific airway conductance
SPSS	Statistical Package for Social Science
SVC	Slow vital capacity
TLC	Total lung capacity
TLCO(c)	Transfer factor of the lung for carbon monoxide (corrected for hemoglobin concentration)
TLCOc/VA	Transfer coefficient for carbon monoxide (corrected for hemoglobin concentration) = KCOc
VA	Alveolar volume
VC	Largest vital capacity
W	Weeks
Yr(s)	Year(s)

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Curriculum Vitae

The author of this thesis was born on 6 July of 1983 in Yerevan, Armenia. At the age of 11 she emigrated with her family to The Netherlands, where she graduated from high school (Gymnasium Trevianum, Sittard) in 2002 cum laude. From 2002 until 2008 she studied Medicine at the University of Maastricht with a cum laude result. During her Medicine study she worked as 'student-assistant' at the department of Anatomy and Embryology and she got familiar with the health care system at Malta (department of pulmonology, St. Luke's Hospital). Her first research experience at the department of Pulmonology of Maastricht University Medical Centre under supervision of Prof. Dr. G. Wesseling resulted in the writing of an abstract called *'Psychological Functioning and Quality of Life of Cystic Fibrosis Adults and Adolescents'* that was presented at the 22nd Annual North American CF Conference in Orlando, FL., in 2008. After a short clinical experience of 3 months as an internal resident at the department of Pulmonology of Deventer Hospital, she started her PhD research in October of 2008 at the department of Pulmonology of Rijnstate Hospital in Arnhem, which resulted in this thesis. Hereafter she started her specialist training to become a pulmonologist, which consists of two years Internal Medicine (2012-2013, Rijnstate Hospital, Dr. Mattijssen) and four years of Pulmonology (2014-2017, Rijnstate Hospital, Dr. Van den Elshout).
She is married to Erik and they have 1 son (Daniël).