Heart & Lung 42 (2013) 365–371

Contents lists available at SciVerse ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.org

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

Armine G. Minasian, MD, PhD(c) [a,*], Frank J.J. van den Elshout, MD, PhD [a], P.N. Richard Dekhuijzen, MD, PhD [b], Petra J.E. Vos, MD, PhD [a], Frank F. Willems, MD, PhD [c], Paul J.P.C. van den Bergh, MD [c], Yvonne F. Heijdra, MD, PhD [b]

[a] Department of Pulmonary Diseases, Rijnstate Hospital, Wagnerlaan 55, 6815 AD Arnhem, The Netherlands
[b] Department of Pulmonary Diseases, Radboud University Nijmegen Medical Center, Geert Grooteplein-Zuid 10, 6525 GA Nijmegen, The Netherlands
[c] Department of Cardiology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD Arnhem, The Netherlands

ARTICLE INFO

Article history:
Received 17 January 2013
Received in revised form
29 June 2013
Accepted 1 July 2013

Keywords:
Chronic heart failure
Chronic obstructive pulmonary disease
Prevalence
Fixed ratio
Lower limit of normal

ABSTRACT

Background: Using a 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 3 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 a fixed ratio of 0.7.

Introduction

Chronic obstructive pulmonary disease (COPD) frequently co-exists 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

Abbreviations: ABHR, aspecific bronchial hyperreactivity; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATS/ERS, American Thoracic Society/European Respiratory Society; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CS, current smokers; FEV_1/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FS, former smokers; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HF, heart failure; ICD, implantable cardioverter defibrillator; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRC, modified Medical Research Council dyspnea scale; NS, non-smokers; NT-pro-BNP, N-terminal pro-B natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PFT, pulmonary function tests; PY, pack-years.

Conflict of interests: The authors have no conflict of interests to declare.
Funding: This work was supported by an unrestricted grant from GlaxoSmithKline. The funding agency had no involvement in study design, data collection, data analysis, interpretation of data, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

* Corresponding author. Department of Pulmonary Diseases, Rijnstate Hospital, P.O. Box 9555, 6800 TA, Arnhem, Gelderland, The Netherlands. Tel.: +31 (0)6 55890546; fax: +31 (0)88 005 6124.
E-mail address: aminasian@rijnstate.nl (A.G. Minasian).

0147-9563/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.hrtlng.2013.07.002

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 a 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 a 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, a COPD prevalence of 30–44% may have been overestimated in prior studies that used a 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 the 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 6 weeks were included 6 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 3 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 3 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 min 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 bronchodilators 6–24 h 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 h 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-h 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 ($<$100 cigarettes in a lifetime), former ($\geq$3 months ago), or current smoker ($<$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.

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, 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 3 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 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 ratio. None of the 9

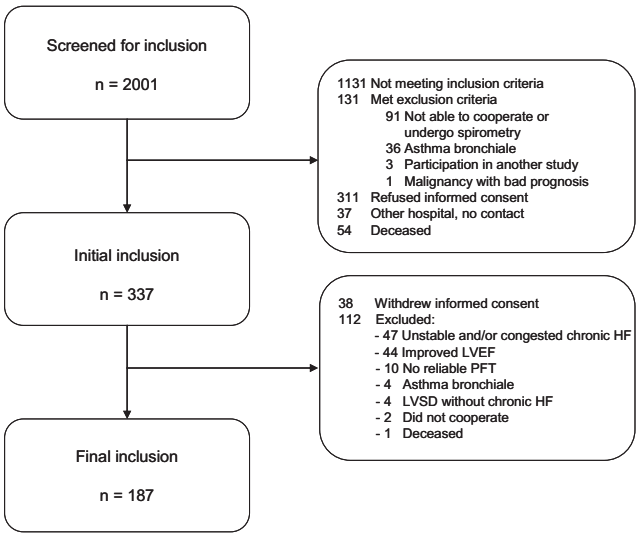

Fig. 1. Flow-diagram of screening and final inclusion of study participants. HF, heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; PFT, pulmonary function tests.

Table 1
Characteristics of patients.

	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 (1 month later) blood samples, respectively.
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.

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)[a]	0 (0)[a]	3 (13)	29 (23)
Current/former smoker	155 (83)	57 (95)[a]	37 (100)[a]	20 (87)	98 (77)
PY, years	24 ± 24	30 ± 28[a]	33 ± 27[a]	24 ± 29	21 ± 21
Symptoms, *n* (%)					
Cough	67 (36)	29 (48)[a]	19 (51)[a]	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)[a]	21 (57)[a,b]	5 (22)	29 (23)
Borg dyspnea scale	0.9 ± 1.2	1.1 ± 1.3[a]	1.5 ± 1.4[a,b]	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)[a,b]	3 (13)	29 (23)
Spirometry					
FEV_1, L	2.5 ± 0.8	2.1 ± 0.7[a]	1.9 ± 0.7[a,b]	2.4 ± 0.6	2.7 ± 0.8
FEV_1, % predicted	88 ± 21	72 ± 22[a]	64 ± 18[a,b]	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[a]	49 ± 8[a,b]	64 ± 3[a]	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.
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.
[a] p-value <0.05 compared with patients without COPD.
[b] p-value <0.05, LLN-COPD compared with potentially misclassified COPD patients.

patients aged between 31 and 50 years were diagnosed with COPD using either definition. COPD prevalence according to the 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).

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 significantly more often had a family history of asthma or COPD when compared with 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 a 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.

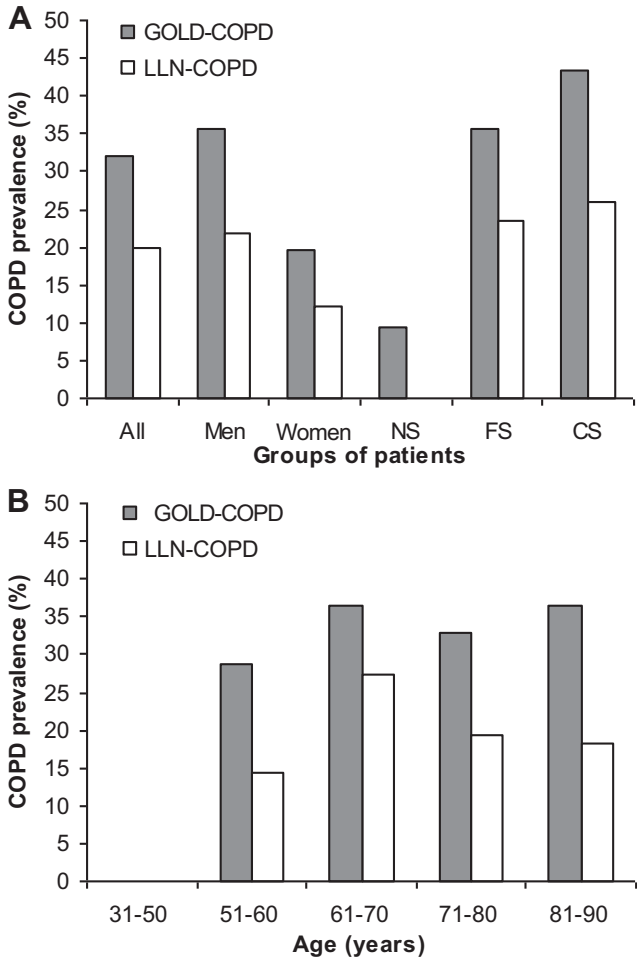

Fig. 2. COPD prevalence as defined by two spirometric criteria and according to (A) gender and smoking status, and (B) age categories. COPD, chronic obstructive pulmonary disease; CS, current smokers; FS, former smokers; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of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

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]

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

Severity class	GOLD-COPD ($n = 60$)			LLN-COPD ($n = 37$)
	All ($n = 60$)	Potentially misclassified: <0.7 but >LLN ($n = 23$)	True COPD: <0.7 and <LLN ($n = 37$)	
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 (%).
ATS/ERS, American Thoracic Society/European Respiratory Society. Other abbreviations are identical to those in the Table 2 legend.

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 a 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.

Acknowledgments

The authors would like to thank the participants in this study for their cooperation. We would also like to thank the nurse practitioners P.A. Ninaber, W.A.M. Janssen, W.H. van Zimmeren-Feijen, and heart failure nurse J.G. Froon-Elferink for their contribution to inclusion of participants and data collection. The authors owe much gratitude to the pulmonary function and clinical chemistry and hematology laboratories as well as the echocardiography and radiology departments for their assistance in data collection. Also, we would like to acknowledge biostatistician A.R.T. Donders for his contribution to statistical analysis. Finally, we thank GlaxoSmithKline for supporting this study by an unrestricted grant.

References

1. Hawkins NM, Petrie MC, Jhund PS, Chalmers GW, Dunn FG, McMurray JJ. Heart failure and chronic obstructive pulmonary disease: diagnostic pitfalls and epidemiology. *Eur J Heart Fail*. 2009;11:130–139.
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHBLI/WHO workshop report. Available at: http://www.goldcopd.org; 2011.
3. Iversen KK, Kjaergaard J, Akkan D, et al. Chronic obstructive pulmonary disease in patients admitted with heart failure. *J Intern Med*. 2008;264:361–369.
4. Mascarenhas J, Lourenco P, Lopes R, Azevedo A, Bettencourt P. Chronic obstructive pulmonary disease in heart failure. Prevalence, therapeutic and prognostic implications. *Am Heart J*. 2008;155:521–525.
5. Macchia A, Rodriguez Moncalvo JJ, Kleinert M, et al. Unrecognised ventricular dysfunction in COPD. *Eur Respir J*. 2012;39:51–58.
6. Boschetto P, Fucili A, Stendardo M, et al. Occurrence and impact of chronic obstructive pulmonary disease in elderly patients with stable heart failure. *Respirology*. 2013;18:125–130.
7. Steinacher R, Parissis JT, Strohmer B, et al. Comparison between ATS/ERS age- and gender-adjusted criteria and GOLD criteria for the detection of irreversible airway obstruction in chronic heart failure. *Clin Res Cardiol*. 2012;101:637–645.
8. Quanjer PH, Enright PL, Miller MR, et al. Open letter: the need to change the method for defining mild airway obstruction. *Prim Care Respir J*. 2010;19:288–291.
9. Celli BR, Halbert RJ. Point: should we abandon FEV/FVC < 0.70 to detect airway obstruction? No. *Chest*. 2010;138:1037–1040.
10. Enright P, Brusasco V. Counterpoint: should we abandon FEV/FVC < 0.70 to detect airway obstruction? Yes. *Chest*. 2010;138:1040–1042 [discussion 42–44].
11. Townsend MC. Conflicting definitions of airways obstruction: drawing the line between normal and abnormal. *Chest*. 2007;131:335–336.
12. Garcia-Rio F, Soriano JB, Miravitlles M, et al. Overdiagnosing subjects with COPD using the 0.7 fixed ratio: correlation with a poor health-related quality of life. *Chest*. 2011;139:1072–1080.
13. Hansen JE, Sun XG, Wasserman K. Spirometric criteria for airway obstruction: use percentage of FEV1/FVC ratio below the fifth percentile, not < 70%. *Chest*. 2007;131:349–355.
14. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of overdiagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J*. 2002;20:1117–1122.
15. Hnizdo E, Glindmeyer HW, Petsonk EL, Enright P, Buist AS. Case definitions for chronic obstructive pulmonary disease. *COPD*. 2006;3:95–100.
16. Miller MR, Quanjer PH, Swanney MP, Ruppel G, Enright PL. Interpreting lung function data using 80 percent of predicted and fixed thresholds misclassifies over 20% of patients. *Chest*. 2011;139:52–59.
17. Roberts SD, Farber MO, Knox KS, et al. FEV1/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. *Chest*. 2006;130:200–206.
18. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax*. 2008;63:1046–1051.
19. Schermer TR, Smeele IJ, Thoonen BP, et al. Current clinical guideline definitions of airflow obstruction and COPD overdiagnosis in primary care. *Eur Respir J*. 2008;32:945–952.
20. Cerveri I, Corsico AG, Accordini S, et al. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax*. 2008;63:1040–1045.
21. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948–968.
22. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure

Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388–2442.
23. Hawkins NM, Petrie MC, Macdonald MR, et al. Heart failure and chronic obstructive pulmonary disease the quandary of beta-blockers and beta-agonists. *J Am Coll Cardiol*. 2011;57:2127–2138.
24. Egred M, Shaw S, Mohammad B, Waitt P, Rodrigues E. Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. *QJM*. 2005;98:493–497.
25. Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Respir J*. 2003;22:268–273.
26. Glaser S, Schaper C, Obst A, et al. Impact of different definitions of airflow limitation on the prevalence of chronic obstructive pulmonary disease in the general population. *Respiration*. 2010;80:292–300.
27. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. *Respiration*. 2005;72:471–479.
28. Shirtcliffe P, Weatherall M, Marsh S, et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J*. 2007;30:232–239.
29. Vollmer WM, Gislason T, Burney P, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Respir J*. 2009;34:588–597.
30. Viegi G, Pedreschi M, Pistelli F, et al. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. *Chest*. 2000;117:339S–345S.
31. O'Hanlon R, O'Shea P, Ledwidge M, et al. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *J Card Fail*. 2007;13:50–55.
32. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377–381.
33. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J*. 1993;16:5–40.
34. http://www.fk.cvz.nl/.
35. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest*. 2004;125:2309–2321.
36. Maak CA, Tabas JA, McClintock DE. Should acute treatment with inhaled beta agonists be withheld from patients with dyspnea who may have heart failure? *J Emerg Med*. 2011;40:135–145.
37. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300:1439–1450.
38. Salpeter SR. Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events?: a synthesis of the available evidence. *Drugs*. 2009;69:2025–2033.
39. Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *N Engl J Med*. 2010;363:1097–1099.
40. Mannino DM, Diaz-Guzman E. Interpreting lung function data using 80% predicted and fixed thresholds identifies patients at increased risk of mortality. *Chest*. 2012;141:73–80.
41. Mannino DM, Sonia Buist A, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax*. 2007;62:237–241.
42. Izquierdo Alonso JL, De Lucas Ramos P, Rodriguez Glez-Moro JM. The use of the lower limit of normal as a criterion for COPD excludes patients with increased morbidity and high consumption of health-care resources. *Arch Bronconeumol*. 2012;48:223–228.
43. Akkermans RP, Berrevoets MA, Smeele IJ, et al. Lung function decline in relation to diagnostic criteria for airflow obstruction in respiratory symptomatic subjects. *BMC Pulm Med*. 2012;12:12.
44. Guder G, Brenner S, Angermann CE, et al. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res*. 2012;13:13.
45. Brusasco V. Spirometric definition of COPD: exercise in futility or factual debate? *Thorax*. 2012;67:569–570.
46. Lamprecht B, Schirnhofer L, Kaiser B, Buist SA, Mannino DM, Studnicka M. Subjects with discordant airways obstruction: lost between spirometric definitions of COPD. *Pulm Med*. 2011;2011:780215.
47. Mohamed Hoesein FA, Zanen P, Sachs AP, Verheij TJ, Lammers JW, Broekhuizen BD. Spirometric thresholds for diagnosing COPD: 0.70 or LLN, pre- or post-dilator values? *COPD*. 2012;9:338–343.
48. Mohamed Hoesein FA, Zanen P, Lammers JW. Lower limit of normal or FEV(1)/FVC $<$0.70 in diagnosing COPD: an evidence-based review. *Respir Med*. 2011;105:907–915.
49. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med*. 1999;159:179–187.
50. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40:1324–1343.