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Serial pulmonary function tests to diagnose COPD in chronic heart failure

Armine G Minasian[1,4*], Frank JJ van den Elshout[1], PN Richard Dekhuijzen[2], Petra JE Vos[1], Frank F Willems[3], Paul JPC van den Bergh[3] and Yvonne F Heijdra[2]

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.

Trial registration: ClinicalTrials.gov Identifier NCT01429376.

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

* Correspondence: aminasian@rijnstate.nl
[1]Department of Pulmonary Diseases, Rijnstate Hospital, Wagnerlaan 55, 6815, AD, Arnhem, The Netherlands
[4]Department of Pulmonary Diseases, Rijnstate Hospital, P.O. Box 9555, 6800, TA, Arnhem, The Netherlands
Full list of author information is available at the end of the article

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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 oedema, 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 dyspnoea scale [26], and 10-point Borg score [27] were used to evaluate quality of life, effect of breathlessness on daily activities, and dyspnoea 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: $FEV_1 \geq 80\%$ 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) [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.

Dyspnoea was defined as resting dyspnoea or dyspnoea 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 ± 10 years and 29 ± 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 ischaemic aetiology 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 dyspnoea (82%). Other respiratory symptoms were less common (cough 36%, sputum 23%,
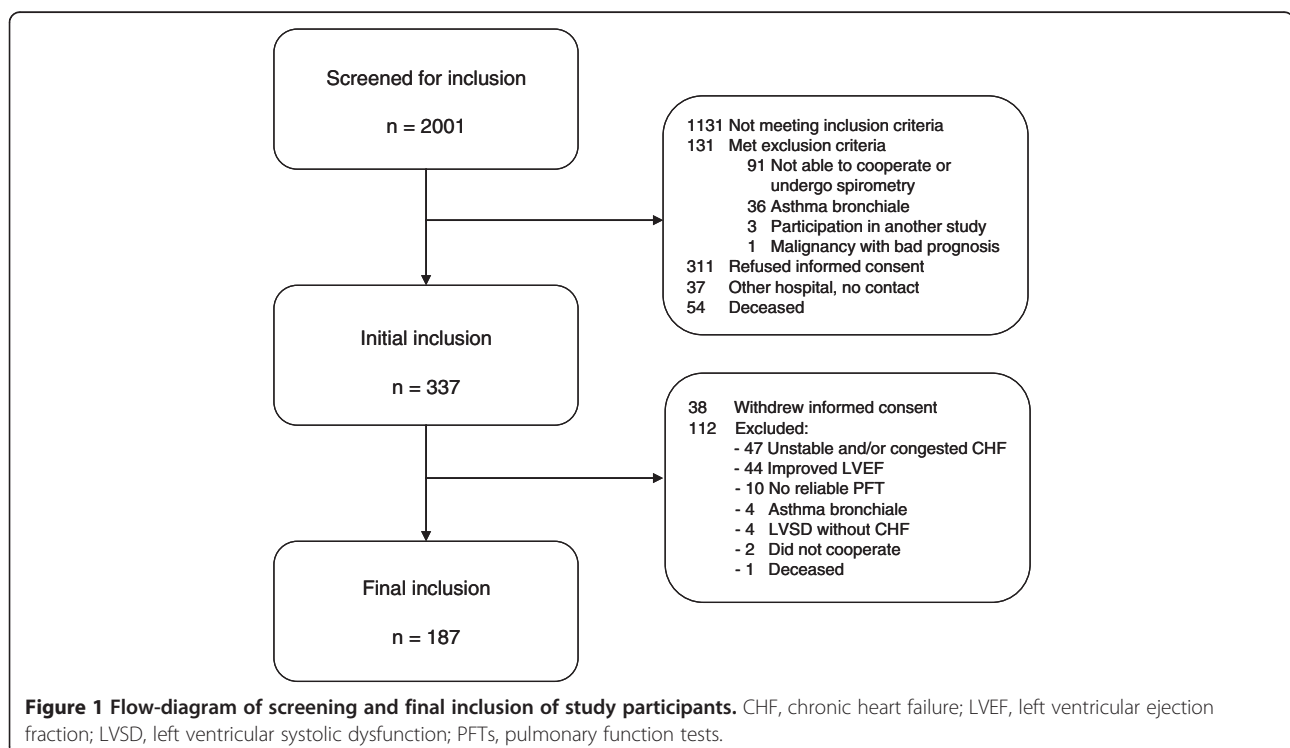

Figure 1 Flow-diagram of screening and final inclusion of study participants. CHF, chronic heart failure; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; PFTs, pulmonary function tests.

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
Ischaemic aetiology	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 resynchronisation 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.

ABHR 29%). The patients received optimised, 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.

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
Dyspnoea	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. 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 dyspnoea scale, *NT-pro-BNP* N-terminal pro-B natriuretic peptide.

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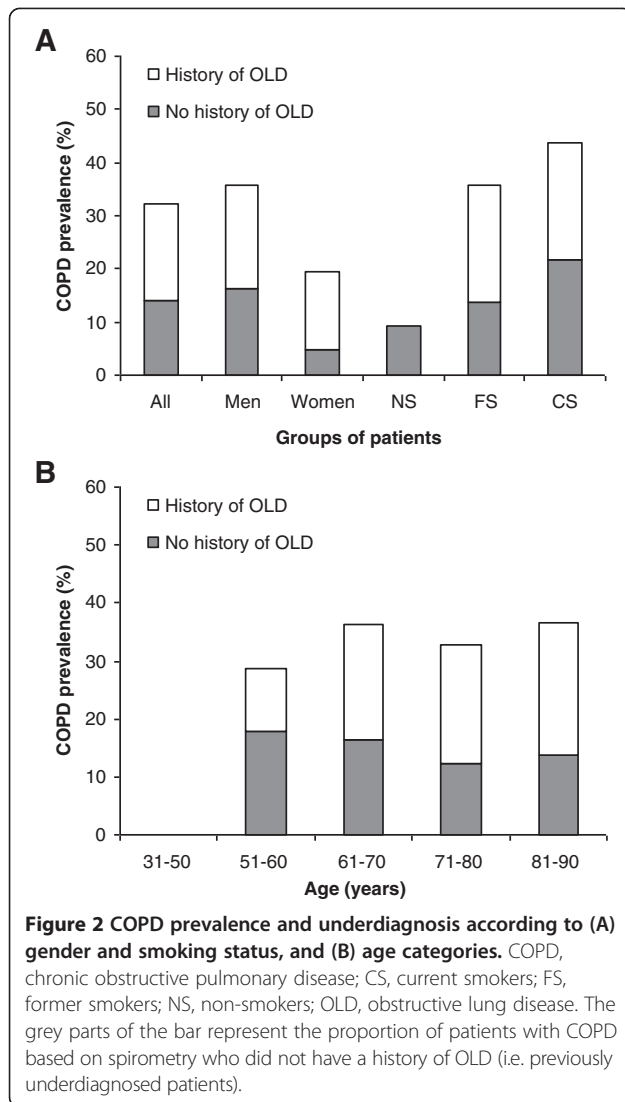
COPD was not associated with a higher NYHA class (p = 0.130). Also, there were no significant correlations between COPD and LVEF (p = 0.401) or NT-pro-BNP (p = 0.251).

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 out-patient 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 month of treatment with tiotropium.

Contrary to our results, initial airway obstruction was found in 19% of patients hospitalised 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

Figure 2 COPD prevalence and underdiagnosis according to (A) gender and smoking status, and (B) age categories. 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).

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

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.

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 realise 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.

Abbreviations

ABHR: Aspecific bronchial hyperreactivity; ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; CABG: Coronary artery bypass grafting; CHF: Chronic HF; COPD: Chronic obstructive pulmonary disease; CRT/ICD: Cardiac resynchronisation therapy; CS: Current smokers; FS: Former smokers; FEV_1/FVC: Ratio of forced expiratory volume in one second to forced vital capacity; GOLD: Global initiative for chronic obstructive lung disease; HF: Heart failure; ICD: Implantable cardioverter defibrillator; ICS/OCS: Inhalation/oral corticosteroids; LVEF: Left ventricular ejection fraction; LVSD: Left ventricular systolic dysfunction; MLHFQ: Minnesota living with heart failure questionnaire; MRC: Modified Medical Research Council dyspnoea scale; NS: Non-smokers; NT-pro-BNP: N-terminal pro-B natriuretic peptide; NYHA: New York Heart Association; OLD: Obstructive lung disease; PCI: Percutaneous coronary intervention; PFT: Pulmonary function tests; PY: Pack-years; SD: Standard deviation; SPSS: Statistical package for social science.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AG contributed to the conception and design of the study, inclusion of participants, acquisition of the data, statistical analysis and interpretation of the data, and drafting of the manuscript. AG had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. FJJ, PNR, and YF contributed to the conception and design of the study, interpretation of the data, critical revision of the manuscript for important intellectual content, and supervision of the study. PJE contributed to the conception and design of the study, interpretation of the data, and critical revision of the manuscript for important intellectual content. FF contributed to the conception and design of the study, inclusion of participants, acquisition of the data, interpretation of the data, and critical revision of the manuscript for important intellectual content. PJPC contributed to the acquisition of the data and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Institutions at which the work was performed

Department of Cardiology, Rijnstate Hospital, Wagnerlaan 55, 6815 AD, Arnhem, The Netherlands.
Department of Cardiology, Rijnstate Hospital, Hunneveldweg 14, 6903 ZN, Zevenaar, The Netherlands.

Author details

[1]Department of Pulmonary Diseases, Rijnstate Hospital, Wagnerlaan 55, 6815, AD, Arnhem, The Netherlands. [2]Department of Pulmonary Diseases, Radboud University Nijmegen Medical Centre, Geert Grooteplein-Zuid 10, 6525, GA, Nijmegen, The Netherlands. [3]Department of Cardiology, Rijnstate Hospital, Wagnerlaan 55, 6815, AD, Arnhem, The Netherlands. [4]Department of Pulmonary Diseases, Rijnstate Hospital, P.O. Box 9555, 6800, TA, Arnhem, The Netherlands.

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