Impact of COPD exacerbations

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Content

Impact of COPD exacerbations on peripheral muscle strength and exercise capacity

A systematic review

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SAMENVATTING

Achtergrond: Acute exacerbaties bij chronic obstructive pulmonary disease (AECOPD) variëren qua intensiteit en frequentie tussen patiënten en gedurende het individuele ziektebeloop. AECOPD's worden geassocieerd met toegenomen ontstekingsactiviteit, afname van ziektespecifiek kwaliteit van leven, toegenomen luchtwegobstructie en een snellere afname van longfunctie. Over de impact van een AECOPD op de perifere spierkracht en het inspanningsvermogen is weinig bekend. Doel van deze studie is het geven van een literatuuroverzicht van publicaties die de impact van een AECOPD op de perifere spierkracht en/ of het inspanningsvermogen beschrijven.

Methode: Geven van een systematisch literatuuroverzicht van studies die zijn verzameld door middel van zoekacties in vier electronische databases en handmatige zoekacties in bibliografieën. Studies die de impact beschrijven van een AECOPD op perifere spierkracht en/of inspanningsvermogen, waarbij gebruik is gemaakt van meetinstrumenten die geschikt zijn voor gebruik binnen de COPD zorg, zijn geïncludeerd.

Resultaten: Negen studies zijn opgenomen in deze review. Deze studies laten zien dat AECOPD's een korte termijn impact lijken te hebben op inspanningsvermogen en perifere spierkracht. De impact van een AECOPD op perifere spierkracht en inspanningsvermogen op de lange termijn blijft onduidelijk.

Conclusie: De huidige literatuur laat zien dat AECOPD's mogelijk een impact hebben op het niveau van perifere spierkracht en inspanningsvermogen. Grote prospectieve cohort-studies, met zowel een korte termijn meting (direct na een AECOPD) als een lange termijn meting (>3 maanden) moeten worden gedaan om de kennis van de impact van AECOPD's op perifere spierkracht en inspanningsvermogen te vergroten.

ABSTRACT

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) vary in severity and frequency both between patients and during the course of a patients' illness. AECOPDs are associated with increased inflammation, decreased disease specific quality of life, increased airflow obstruction and a faster decline in lung function. However little is known about the impact of an AECOPD on peripheral muscle strength and exercise capacity. The aim of this study is to provide a review of the current literature which describes the impact of AECOPDs on peripheral muscle strength and/or exercise capacity.

Methods: Systematic review of studies conducted by searches in four electronic databases and hand-searches in bibliographies. Studies which describe the impact of an AECOPD on peripheral muscle strength and/or exercise capacity using validated measurement instruments appropriate for use in COPD were included. Two reviewers independently performed a literature search and extracted the data, disagreements were resolved by consensus.

Results: Nine studies were included in this review. These studies show that there is an indication that AECOPDs have a short-term impact on exercise capacity and peripheral muscle strength. The long-term impact of an AECOPD on peripheral muscle strength and exercise capacity remains unclear.

Conclusion: Evidence suggests that there might be an impact of AECOPDs on peripheral muscle strength and exercise capacity. Large prospective cohort-studies with both short-term assessment (directly after AECOPD) as well as long-term assessment (>3 months) need to be performed to increase better understanding of the impact AECOPDs on peripheral muscle strength and exercise capacity.

Keywords: Chronic Obstructive Pulmonary Disease, exacerbations, peripheral muscle strength, exercise capacity

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive chronic disease which results in substantial economic and social burdens to society [1, 2]. COPD is expected to become the number one cause of respiratory-related disability in the

world by the year 2020 [3]. COPD is characterized by an inexorable decline in respiratory function, health status and exercise capacity [4]. Stable day-to-day symptoms might be interrupted by acute exacerbations of chronic obstructive pulmonary disease (AECOPD) which is characterized by increased sputum volume, color and consistency in combination with increased dyspnea [5]. AECOPDs vary in severity and frequency both between patients and during the course of a patient's illness [6]. Exacerbations have been defined using a complex of worsening respiratory symptoms alone (symptom-based) or by respiratory symptoms in combination with an event like the prescription of medication by a family doctor or hospital admission [7]. The most frequently used definition for AECOPDs is the "consensus definition" formulated at the Aspen Lung Conference in 2000 where AECOPDs have been defined as: "a sustained worsening of the patient's condition, from stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD" [8]. AECOPDs might be caused by environmental pollutants (e.g. cigarette smoke) [9] but generally by respiratory infections [10]. Most patients with COPD experience at least one AECOPD per year [11, 12], which causes a significant increase in mortality, emergency room visits and higher health care costs [13-15]. The number of exacerbations per year might be underestimated, because exacerbation rates reported for symptom-based studies tend to be higher compared with the number reported in event-based studies. This suggests that about 50% of real exacerbations are not reported to the research team [16, 17]. AECOPDs are associated with increased inflammation [18-20], decreased disease specific quality of life [16], increased airflow obstruction and a faster decline in lung function [12]. AECOPDs incorporate factors which might contribute to muscle weakness and decreased exercise capacity, including inflammation, immobility, negative nitrogen balance and the administration of corticosteroids [21]. Peripheral muscle strength and exercise capacity are both important modalities in COPD care. Peripheral muscle weakness has been associated with exercise limitation [22], impaired quality of life [23, 24] and increased health care consumption [24]. It has been shown that there is a significant relationship between exercise capacity and survival in COPD patients [25] and the risk of hospital admission [26]. Impact of AECOPDs on peripheral muscle strength and exercise capacity has never been reviewed. This can be used in developing and evaluating therapeutic interventions aimed at rehabilitative care including physical exercise, patient education focusing on self-management strategies and

psychological support [27]. The aim of this study is to provide a review of the current literature which describes the impact of AECOPDs on peripheral muscle strength and exercise capacity.

METHODS

Data sources and searches

A computer-based search was performed querying Ovid MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE (Experta Medica) and the Cochrane Library for original research articles. Searches within the databases were conducted using several combinations of the following Mesh headings and search-terms: functional status, functional performance, physical performance, motor activity [Mesh], physical endurance [Mesh], endurance, physical mobility, mobility, physical fitness [Mesh], fitness, muscle strength [Mesh], disease exacerbation, exacerbation, "AECOPD", "ECOPD", pulmonary disease, chronic obstructive [Mesh], Chronic Obstructive Pulmonary Disease, lung diseases, obstructive [Mesh], lung diseases [Mesh], lung diseases, Airway Obstruction [Mesh], pulmonary emphysema [Mesh], emphysema [Mesh], bronchitis, chronic [Mesh], bronchitis [Mesh]. The databases have been searched from each database inception until June 2009. A detailed search strategy is available on request. In addition, reference lists of relevant articles were searched to identify articles for this study not identified in the database search.

Criteria for considering studies for this review

The following criteria were used to select articles for the inclusion in this review; 1) studies must have a focus on AECOPD; 2) a study population in which more than 90% had a clinical diagnosis of COPD; 3) peripheral muscle strength and/or exercise capacity were assessed using validated measurement instruments appropriate for use in COPD. Articles published in languages other than English, abstracts, letters and reviews were excluded.

Study Selection

All retrieved articles were stored in a Refworks file©. Duplicated records from the various databases were removed. Two researchers (AK and DB) independently

assessed the titles and abstracts of the identified studies and recorded their considerations. Both reviewers compared their considerations and resolved their disagreements by consensus. A third investigator (MvH) was consulted in case of disagreement between the two assessors. Full texts of all potentially eligible papers were evaluated independently by two reviewers (AK en DB) and the final decision to be included in this review was made based on the eligibility criteria for this study. Once more, both researchers tried to reach consensus and in case of disagreement a third (MvH) assessor made the final decision for inclusion in this study. There was no blinding of names of authors, institutions or outcomes during the study selection in this review. Results were summarized in predefined structured tables and placed in a Microsoft Excel file.

RESULTS

Article identification

The study selection process and agreement on study inclusion is showed in Figure 1. After excluding duplicates, 336 unique publications were identified which were independently reviewed as previously described. These publications were reduced to 36 potentially eligible studies after screening on title and abstract. One study has been excluded because less than 90% of the study population had a clinical diagnosis of COPD. Fifteen studies had no focus on AECOPD and eleven studies did not measure exercise capacity or peripheral muscle strength. After assessing these 36 potentially relevant studies, nine [28-36] articles were included in this review. All disagreement could be resolved by consensus between the first two reviewers. It has to be noticed that the included studies largely varied in their objectives and assessment methods, however all studies investigated muscle strength or exercise capacity at one or more endpoints in patients with documented AECOPD and were therefore eligible for this systematic review.

Study design and patient population

Four studies [28, 29, 34, 35] were prospective cohort studies, three [31-33] had a cross-sectional design and two studies [30, 36] were randomized controlled trials (Table 1). The studies were divided in methods used for identification of participants. Three studies [30, 35, 36] recruited patients presenting in the hospital or emergency room

because of deterioration in their respiratory status and three studies included clinically stable patients [28, 29, 34]. Two studies compared hospitalized- with clinically stable patients and healthy elderly [31, 33] and one study compared hospitalized COPD patients only with clinically stable patients [32]. All studies investigated COPD patients with an average age between 60-70 years old. There were no large differences in Forced Expiratory Volume in one second percentages predicted (FEV_1%pred.) between the subjects in the studies (Range FEV_1%pred. = 32-50 for patients with COPD). All studies used an event based approach to identify exacerbations, except the studies conducted by Cote- [34] and Carr et al. [29] who used a symptom-based definition. The Anthonisen definition [5] and the Rodriguez-Roisin definition [8] were most frequently used to identify AECOPDs.

Peripheral muscle strength and exacerbations

Seven studies measured peripheral muscle strength [28, 30-33, 35, 36] (Table 1). Hopkinson et al. [28] recruited 64 clinically stable COPD patients and studied this cohort on two occasions one year apart. Quadriceps maximum voluntary contraction (QMVC) was measured with subjects seated, trying to extend their dominant leg as hard as possible against an inextensible strap connecting their ankle to a strain gauge. These isometric measurements were performed at baseline and after one year. Clinical information including treatment and the number of exacerbations in the previous year were reported. In this cohort QMVC declined significantly ($p<0.05$) after one year follow-up (%predicted = 62.3) compared with baseline level (%pred. = 66.3). Decrease in QMVC was not associated with exacerbation frequency in this cohort. In the study which was conducted by Pitta et al. [35], QMVC was measured using a Cybex Norm Dynanometer. [37] from 24 patients at days 3 and 8 of hospitalization and one month after discharge. They reported a significant ($p<0.05$) decrease in QMVC between day 3 (%pred. = 72) and day 8 (%pred. = 64) of hospitalization. QMVC significantly ($p<0.01$) improved one month after discharge (%pred. =70), but did not return to baseline level. Crul et al. [31] conducted a study where 14 hospitalized patients were compared with 11 clinically stable patients and 7 healthy elderly. QMVC and hand grip strength (HGS) were measured (methods used were not reported) at days 3 and 8 of hospitalization. Stable COPD patients and sedentary elderly were measured in an outpatient setting. At day 3 of hospitalization, patients had significant lower QMVC (%pred. = 59) compared with stable patients (%pred. =

78) and healthy elderly (%pred. = 87). HGS was lower at day 3 of hospitalization in hospitalized patients (%pred. = 87) compared with clinically stable patients (%pred. = 100) and healthy elderly subjects (%pred. = 108). However this difference was not statistically significant. During hospitalization QMVC (%pred.) decreased by 6% in 11 out of 14 hospitalized patients. Spruit et al. [33] investigated the clinical course of peripheral muscle strength during an AECOPD. HGS [38] and QMVC (Cybex Norm Dynamometer) [37] were measured from 34 hospitalized patients and compared with 13 clinically stable patients and 10 healthy sedentary elderly. Hospitalized patients had at day three of hospitalization significant ($p<0.05$) lower QMVC (%pred. = 66) and HGS (%pred. = 86), compared with clinically stable patients (QMVC %pred. = 86; HGS %pred. = 104) and healthy elderly (QMVC %pred. = 103; HGS %pred. = 112). QMVC decreased by a mean of 5% of the predicted value (95% CI -22 to 8, $p=0.05$) between days 3 and 8 of hospitalization. There were no significant changes in HGS reported during hospitalization. After hospitalization (90 days), QMVC significantly ($p=0.008$) recovered (mean 6% of predicted value (95% CI -1 to 23) $p=0.008$) but did not return to baseline level. In a second study conducted by Spruit et al. [32] 16 clinically stable COPD patients were compared with 14 hospitalized patients during the third day of hospitalization. QMVC (Cybex Norm Dynamometer) [37] was measured according to Gosselink et al. [22] They reported no statistically significant ($p=0.13$) differences in QMVC between stable- (%pred. = 75) and hospitalized patients (%pred. = 67). Saudny-Unterberger et al. [36] and Vemeeren et al. [30] both conducted a randomized controlled trial in which hospitalized patients who received extra nutritional support were compared with hospitalized patients who received usual care. Saudny-Unterberger et al. [36] measured HGS at baseline and two weeks post-admission using a handgrip dynamometer. They did not report significant changes ($p>0.05$) in HGS during hospitalization within the control-group (change = 0.375 kg) or within the treatment-group (change = -0.869 kg). Saudny-Unterberger et al. did not report significant between group differences ($p=0.400$) in HGS during the course of hospitalization. Vemeeren et al. [30] measured QMVC using a Cybex II + dynamometer and HGS with the use of a handgrip dynamometer at hospital admission and days 4 and 8 of hospitalization. At baseline there were no significant ($p>0.05$) differences in HGS between the control-group (HGS = 28 kg) and the intervention group (HGS = 28 kg). QMVC was not measured at baseline because the majority of the hospitalized patients could not perform a valid quadriceps strength

test. There were no significant (p>0.05) changes reported in QMVC and HGS between days 4 and 8 of hospitalization in the intervention- (change QMVC (Nm) = 3; change HGS (kg) = 0) neither in the control group (change QMVC (Nm) = 2; change HGS (kg) = 0).

Exercise capacity and exacerbations

In five studies [29, 30, 32, 34, 36] exercise capacity was measured (Table 1). Carr et al. [29] included 53 clinically stable COPD patients who completed pulmonary rehabilitation in a 6 month observational study. Patients were taught to identify AECOPDs and were asked to call the research coordinator as soon as possible in case of a moderate or severe exacerbation. The 6-min walk test (6MWT) was performed at baseline and 2 to 4 weeks after the onset of an AECOPD. Subjects who remained event free were followed up for 6 months, with baseline measurements repeated after 3 and 6 months. Patients who relapsed had a significant (p=0.018) lower 6-min walk distance (6MWD) at baseline (6MWD = 350 m) compared with patients who remained event free (6MWD = 416 m). There was a significant (p<0.001) decrease in 6MWD noted 2-4 weeks after AECOPD onset (mean change 6MWD = 59 meter). No significant differences (p>0.05) were found at 3 (6MWD = 418 m) and 6 months (6MWD = 405 m) compared with baseline level in the group who remained event-free. Cote et al. [34] included 205 clinically stable COPD patients and assessed a 6MWT at baseline and in case of absence of an AECOPD after 3 and 6 month. Patients were taught to identify an AECOPD and asked to contact the clinic within 48 hours after AECOPD onset. 6MWT was assessed within 48 hours after AECOPD onset and repeated every 6 months. At baseline there were no significant (p=0.91) differences in 6MWD between patients who relapsed (6MWD = 359 m) and patients who remained event-free (6 MWD = 354 m). Directly after AECOPD patients had a significant (p=0.00004) reduction in 6MWD (change = -72 m) compared with baseline level which did not recover after 1 (change = -49 m) and 2 (change = -74 m) years. There were no significant changes in 6MWD (p=0.96) after 1 year (change = 17 m) and 2 years (change = 1 m) within the group who remained event free. In the study conducted by Pitta et al. [35], a 6MWT was performed at day 8 of hospitalization because of disease deterioration and one month after discharge. They reported a significant improvement (p=0.01) of 6MWD between day 8 (6MWD = 268 m) of hospitalization and one month (6MWD = 332 m) after AECOPD.

Spruit et al. [32] compared 16 clinically stable COPD patients and 14 patients who were hospitalized because of deterioration of their respiratory status. At baseline 6MWD was assessed, a symptom-limited peak exercise test was performed at day 8 of hospitalization and a symptom-limited constant-work-rate test was performed 2-3 days later. Compared with stable patients (6MWD = 439 m), hospitalized patients (6MWD = 251 m) had a significant ($p=0.04$) lower 6MWD at baseline. In both groups cycling exercise bouts were limited by reaching the maximal voluntary ventilation. Values obtained at the end of the symptom-limited peak exercise test (heart rate, ventilation and oxygen uptake) were comparable to the values at the end of the constant-work-rate test in both groups. There were no statistically significant ($p>0.05$) differences reported between both groups in cycle performance.

Saudny-Unterberger et al. [36] measured in their randomized controlled trial where 10 hospitalized patients who received extra nutritional support were compared with a control group (n=14) the 6MWD after two weeks hospitalization. After two weeks of hospitalization there were no significant ($p=0.288$) differences in 6MWD between the control- (6MWD = 201 m) and placebo-group (6MWD = 253 m). There was no within group analyses performed, because a number of subjects could not perform a 6MWT at baseline.

DISCUSSION

This systematic review indicates that AECOPDs have a short-term impact on exercise capacity and peripheral muscle strength. The long-term impact of an AECOPD on peripheral muscle strength and exercise capacity remains unclear. To our knowledge this is the first systematic review which describes the effect of an AECOPD on peripheral muscle strength and exercise capacity. Impacts of AECOPDs on other outcomes in COPD have previously been described and show similar results. Schmier et al. [39] systematically reviewed studies which describe the impact of acute exacerbations of chronic bronchitis (AECB) on health related quality of life (HRQL). This study showed that exacerbations lead to substantial reductions in HRQL, both in physical as well as in other domains. Another review conducted by Niewoehner [40] described the interrelationship between lung function and COPD exacerbations. They showed that exacerbations are associated with short-term decreases in the FEV_1 and with other measures of lung function.

Three studies [31, 33, 35] which were included in this study revealed that peripheral muscle strength decreased during hospitalization. A possible explanation for these outcomes is that patients who are hospitalized because of an AECOPD are more sedative. In healthy elderly subjects, quadriceps weakness has shown to occur in relatively short periods of bed rest (10 days) [41]. Another explanation is an increased systemic inflammation [33] which occurs during an AECOPD and the administration of corticosteroids [42] which might contribute to peripheral muscle weakness.

After AECOPD a reduction of 6MWD was reported in two studies [29, 34] which was present in the short as well as in the middle-long term. Surprisingly the study conducted by Spruit et al. [32] showed equal values obtained at the end of the symptom-limited peak exercise test and the symptom-limited constant-work-rate test (heart rate, ventilation and oxygen uptake) between hospitalized and clinically stable COPD patients. It is plausible that there are also subjective factors which might contribute to a decrease in 6MWD (e.g. dyspnea, general discomfort).

An explanation for the decline in 6MWD in the middle long term might be that patients with COPD tend to be more sedative after an AECOPD [35] and spent less time outdoors [43] which might result in lower exercise capacity.

Four studies [29, 31-33] reported differences at baseline in peripheral muscle strength and/or exercise capacity between patients with stable COPD and patients who experienced an AECOPD. It is possible that the lower exercise capacity and peripheral muscle strength was already present before the event of an AECOPD. Quadricps weakness and exercise capacity before exacerbation onset have shown to be related with AECOPDs and health-care utilization [24, 26] which might have biased results.

Most studies used computarized dynamometers (e.g. Cybex) to measure peripheral muscle strength. A disadvantage of these instruments is that they are not portable and not available in most (primary care) practices. A useful, reliable [44] instrument to measure peripheral muscle strength might be a Hand-Held dynamometer (e.g. MicroFet). This instrument might be used in symptom-based studies, because it is possible to take measurements in home situations, directly after AECOPD onset. Vermeeren et al. [30] reported that the majority of the hospitalized patients could not perform a valid quadriceps strength test during the first days of hospitalization. An additional advantage of a Hand-Held dynamometer is that it might be easier for a patient to perform a valid quadriceps test during the first days of hospitalization.

A disadvantage of this review was the small number of participants in the included studies. Most studies had a small sample-size which resulted in a lack of statistical power for detection of change in peripheral muscle strength and/ or exercise capacity. There was large variability in study design and methods of peripheral muscle strength and exercise capacity assessment. Therefore it was not possible to perform meta-analysis or to make a best evidence synthesis. Nevertheless this study increased knowledge about the impact of an AECOPD on peripheral muscle strength and exercise capacity. Future research need to be performed to increase knowledge of the impact of AECOPDs on peripheral muscle strength. Large prospective-cohort studies with both short-term assessment (directly after AECOPD) as well as long-term assessment (>3 months) need to be performed to increase better understanding of the impact AECOPDs on peripheral muscle strength and exercise capacity.

Confounding factors which might contribute to peripheral muscle weakness and reduced exercise capacity need to be addressed in future studies. This might contribute to the development of rehabilitation strategies and might decrease bias in future trials aimed at peripheral muscle strength and/or exercise capacity in future trials. In conclusion this study has showed that AECOPDs have an short-term impact on exercise capacity and peripheral muscle strength, but there is no indication that there is a long-term impact on these outcomes.

Table 1: Characteristics of included studies

Reference	Study design, population, country	Methods and instrumentation*	Findings
Carr et al. 2007	Prospective cohort study Patients with clinically stable COPD (N=53) Mean age: 69 ± 8 Gender: 50%male Mean FEV_1 (% pred.) = 38 ± 16 (11-80) Canada	6MWT at baseline, after 3, 6months and 2-4 weeks after AECOPD onset. Definition exacerbation: Anthonisen Follow-up: 6 months	Baseline: Lower 6MWD in relapsed- (6MWD = 350m) compared with event-free group (6MWD = 416m), (p=0.018) After AECOPD (2-4 weeks): Reduction in 6MWD (change = -59m) compared with baseline (p<0.001) No changes in 6MWD at 3 (6MWD = 418m) and 6months (6MWD = 405m) compared with baseline in the event-free group (p>0.05)
Cote et al. 2007	Prospective cohort study Relapsed COPD patients (N=130) Mean age: 67 ± 9 Gender: 94%male Mean FEV_1 (% pred.) = 39.5 ± 15 Clinically stable COPD patients (N=75)	6MWT at baseline, after 6 months and 48 after AECOPD onset. Definition exacerbation: Rodriguez-Roisin definition Follow-up: 24 months	Baseline: No difference between the relapsed- (6MWD = 359m) and the event-free group (6MWD = 354m), (p=0.91) After AECOPD (48hours): Reduction in 6MWD (change = -72m), without significant improvement after 2 years follow-up (p=0.0004) No change in 6MWD at 1 (change = 17m) and 2 (change = 1m) years follow-up in the event-free group (p=0.96)

	Mean age: 67 ± 9 Gender: 96%male Mean FEV_1 (% pred.) = 48.5 ± 16 United States		
Pitta et al. 2006	Prospective cohort study Hospitalized COPD patients (N=24) Median age: 68 (IQR:60-78) Gender: 92%male Mean FEV_1 (% pred.) = 44 ± 17 Belgium	QMVC at days 3 and 8 and 1month after hospitalization 6MWT at day 8 of hospitalization and 1month after discharge. Definition exacerbation: Anthonisen Follow-up: 1 month	Hospitalization: Decrease in QMVC between days 3 (%pred. = 72) and 8 (%pred. = 64) ($p<0.05$) After discharge (1month): QMVC improved (%pred.= 70) ($p<0.01$). Improvement of 6MWD (change = 64m), ($p=0.01$)
Hopkinson et al. 2007	Prospective cohort study Patients with clinically stable COPD (N=64) Mean age: 62 ± 9 Gender: 66%male Mean FEV_1 (% pred.) = 36 ± 18	QMVC at baseline and 1 year Definition exacerbation: Discrete episodes of worsening of respiratory symptoms leading to treatment with antibiotics Follow-up: 12 months	One year: Decline in QMVC (%pred. = 62.3) compared with baseline (%pred. = 66.3) but this was not associated with exacerbation frequency ($p<0.05$)

	United Kingdom		
Spruit et al. 2003	Cross-sectional comparative study Hospitalized COPD patients (N=34) Mean age: 69 ± 7 Mean FEV_1 (% pred.) = 40 ± 17 Clinically stable COPD patients (N=13) Mean age: 68 ± 10 Mean FEV_1 (% pred.) = 50 ± 15 Healthy elderly subjects (N=10) Mean age: 68 ± 8 Mean FEV_1 (% pred.) = 107 ± 10 Belgium	HGS and QMVC at days 3, 8 and 90 days after hospitalization Definition exacerbation: Anthonisen Follow-up: 90 days	Hospitalization (day 3): hospitalized patients had lower peripheral muscle strength (QMVC %pred.=66; HGS %pred. =86) compared with clinically stable patients (QMVC %pred. = 86; HGS %pred. =104) and healthy elderly (QMVC %pred. = 103; HGS %pred. = 112) (<0.05) Hospitalization (days 3-8): QMVC decreased by a mean of 5% of predicted value (95% CI- 22 to 8, p=0.05), no significant changes in HGS reported. After discharge (90 days): QMVC increased (mean 6% of predicted value (95% CI-1 to 23)p=0.008)
Spruit et al. 2007	Cross-sectional comparative study Hospitalized COPD patients (N=14)	QMVC and 6MWT at baseline, symptom-limited peak exercise test at day 8 of hospitalization, symptom-limited constant-work-rate test (2-3 days after the peak test)	Hospitalization (day 3): No difference in QMVC between stable- (%pred. = 75) and hospitalized patients (% pred. = 67), (p=0.13). Lower 6MWD in hospitalized- (6MWD = 251m) compared with stable patients (6MWD = 439m), (p=0.04).

	Mean age: 65 (IQR: 59-74) Gender: 71%male Mean FEV_1 (% pred.) = 41 (IQR: 33-54) Clinically stable COPD patients (N=16) Mean age: 63 (IQR: 60-75) Gender: 82%male Mean FEV_1 (% pred.) = 45 (IQR: 33-58) Belgium	Definition exacerbation: Rodriguez-Roisin Follow-up: 11 days	Values obtained at the end of the symptom-limited peak exercise- and the constant-work-rate test were comparable in both groups (heart rate, ventilation and oxygen uptake).
Crul et al. 2007	Cross-sectional comparative study Hospitalized COPD patients (N=14) Mean age: 68 ± 8 Gender: 92%male Mean FEV_1 (% pred.) = 44 ± 17 Clinically stable COPD patients (N=11) Mean age: 68 ± 9	QMVC and HGS, days 3 and 8 of hospitalization. Definition exacerbation: Increased sputum ,symptoms of dyspnea, sputum volume and purulence and cough frequency for at least 48h Follow-up: 8 days	Baseline (day3): Lower QMVC in hospitalized- (%pred. = 59) compared with stable patients (% pred. = 78) and healthy elderly (%pred. = 87), ($p<0.05$). Lower (non-significant) HGS in hospitalized - (%pred. = 87) compared with clinically stable patients (%pred. = 100) and healthy elderly subjects (%pred. = 108) Hospitalization (days 3-8): QMVC (%pred.) decreased by 6% in 11 out of 14 hospitalized patients.

	Gender: 90%male Mean FEV_1 (% pred.) = 52 ± 15 Healthy elderly subjects (N=7) Mean age: 70 ± 7 Gender: 100%male Mean FEV_1 (% pred.) = 108 ± 11 Belgium		
Saudney-Unterberger et al. 1997	Randomized controlled trial Hospitalized COPD patients, nutritional support (N=10) Mean age: 69 ± 4 Gender: 70%male Mean FEV_1 (% pred.): 35 ± 4 Hospitalized COPD patients, placebo (N=14) Mean age: 69 ± 2 Gender: 57%male Mean FEV_1 (% pred.): 33 ± 4 Canada	HGS (days 4 and 8 of hospitalization) and 6MWD (2 weeks post-admission) Definition exacerbation: Hospital admission for deterioration of symptoms Follow-up: 2 weeks	Baseline: No differences in HGS between intervention- (HGS= 29.71 kg) and control-group (HGS = 25.95 kg), (p=0.385) Hospitalization (days 4-14): No changes in HGS within control- (change = 0.375 kg) and treatment-group (change = -0.869 kg), (p>0.05). No between-group differences in HGS (p=0.400). No differences in 6MWD between the control-group (6MWD = 201m) and placebo-group (6MWD = 253m), (p=0.288).

Vermeeren et al. 2004	Randomized controlled trial Hospitalized COPD patients, nutritional support (N=23) Mean age: 66 ± 8 Gender: 61%male Mean FEV_1 (% pred.) = 32 ± 12 Hospitalized COPD patients, placebo (N=24) Mean age: 65 ± 10 Gender: 75%male Mean FEV_1 (% pred.) = 34 ± 12 The Netherlands	HGS at baseline QMVC and HGS at days 4 and 8 of hospitalization	Baseline: No difference in HGS between the control- (HGS = 28 kg) and intervention-group (HGS = 28 kg), ($p>0.05$). Hospitalization (days 4-8): No changes in QMVC and HGS in the intervention- (change QMVC (Nm)= 3; change HGS (kg) = 0) and the control-group (change QMVC (Nm) = 2, change HGS (kg) = 0), ($p>0.05$).

*Outcomes on the level peripheral muscle strength or exercise capacity are represented (Forced Expiratory Volume in one second = FEV_1, 6 MWT = 6-min walk test, 6MWD = 6-min walk distance, QMVC = Quadriceps maximum voluntary strength , HGS = Handgrip strength)

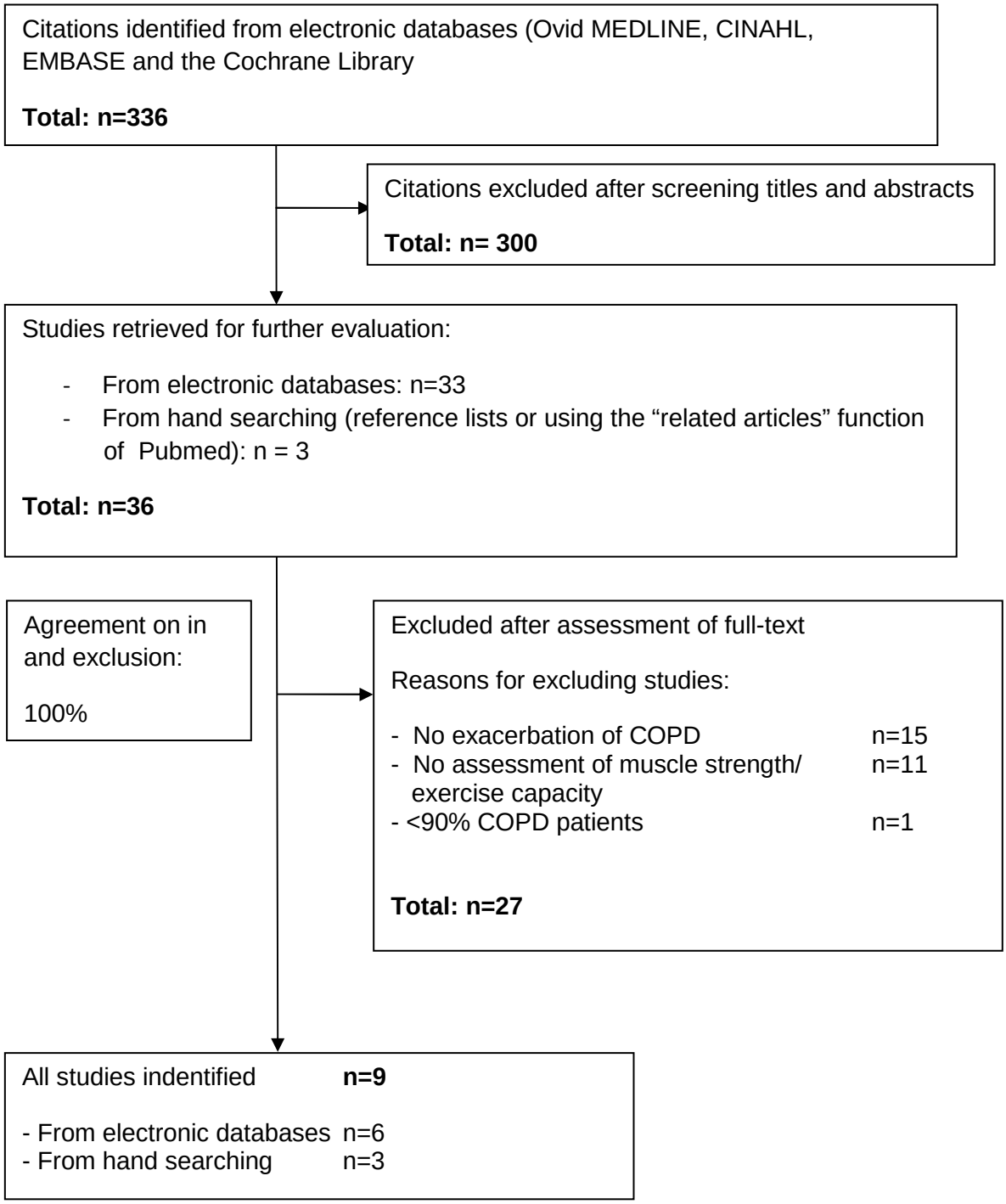

Figure 1: Study flow from identification to final inclusion of studies

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Impact of COPD exacerbations on patients' health-status compared to stable day-to-day variations

Research article

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SAMENVATTING

Achtergrond: Acute exacerbaties bij chronic obstructive pulmonary disease (AECOPD) hebben een significant negatieve impact op de gezondheidstoestand van een patiënt. De bandbreedte van de dag tot dag variabiliteit van gezondheidsstatus bij stabiele patiënten met COPD en de impact/ hoeveelheid verandering ten tijde van een AECOPD blijft onduidelijk. Deze studie heeft als doel om de stabiele dag tot dag variabiliteit van de gezondheidstoestand van stabiele patienten met chronic obstructive pulmonary disease (COPD) te onderzoeken en gedurende een AECOPD. Secundair doel van deze studie is de verandering in gezondheidsstatus te onderzoeken tijdens een AECOPD.

Design: Een prospectief cohort studie

Methode: Patienten (n=40; man=22; FEV_1%voorspeld=60.41 ± 18.67) met een diagnose COPD (GOLD I-IV) zijn gevraagd om een dagboek bij te houden waarin veranderingen van respiratoire symptomen gedurende de laatste 24 uur werden genoteerd. Een AECOPD werd gedefinieerd op basis van het Anthonisen symptom algoritme. Gezondheidstoestand werd gemeten met de Clinical COPD Questionnaire (CCQ) met een interval van drie dagen. CCQ scores werden retrospectief gelabeled op basis van de aanwezigheid van een AECOPD.

Resultaten: De gemiddelde follow-up tijd gedurende de studie was 110.67(± 27,69) dagen. In totaal zijn 4427 dagen (12.13 jaar) gerapporteerd en zijn 29 exacerbaties (rate 2.39 exacerbaties/jaar) geïdentificeerd. In vergelijking met stabiele COPD nam de gemiddelde CCQ totaalscore ($p=0.004$) en de domeinen functie ($p=0.009$) en symptomen ($p=0.000$) toe. Er was sprake van een klinisch en statitistisch significante impact op gezondheidstoestand direct na het begin van een AECOPD in vergelijking met stabiele perioden. Dit kwam naar voren in de CCQ totaal ($p<0.001$) en – domein scores ($p<0.05$). De maximale afname van gezondheidsstatus gedurende AECOPD lag buiten de normale dag tot dag variaties van gezondheidstoestand tijdens stabiele perioden.

Conclusie: Deze studie laat zien dat AECOPDs een grote impact hebben op de gezondheidstoestand van een patient in vergelijking tot stabiele dag tot dag variateit.

ABSTRACT

Background: Acute exacerbation in chronic obstructive pulmonary disease (AECOPD) have significant negative impact on patients' health-status. The bandwidth of day-to-day variability in health-status in patients with stable COPD and impact / amount of change during the event of an AECOPD remains unclear. This study aims at investigating stable day-to-day variability in health-status of patients suffering from chronic obstructive pulmonary disease (COPD) and during an AECOPD. Secondary aim of this study is to investigate the change in health-status during AECOPD.

Design: A prospective multi-center cohort study.

Methods: Patients (n=40; male=22; FEV_1%predicted=60.41 ± 18.67) with a diagnosis of COPD (GOLD I-IV) were asked to record respiratory symptom change during the past 24 hours on a daily diary card. AECOPD was defined using the Anthonisen symptom algorithm. Health-status was measured on three day intervals using the Clinical COPD Questionnaire (CCQ). CCQ scores were retrospectively labeled according to the presence of an AECOPD.

Results: Mean follow-up time during the study period was 110.67(± 27,69) days. In total 4427 days (12.13 years) were completed and identified 29 exacerbations (rate:2.39 exacerbations/year). Compared with stable COPD, mean CCQ total score ($p=0.004$) and the domains function ($p=0.009$) and symptoms ($p=0.000$) increased in the event of an AECOPD. There was a clinically and statistically significant impact on health-status directly after AECOPD onset compared with stable periods which was represented in the CCQ total ($p<0.001$) and domain scores ($p<0.05$). The maximum deterioration in health-status during AECOPD was beyond day-to-day variations in health-status during stable COPD.

Conclusion: This study shows that an AECOPD has major impact on patients' health-status compared with stable COPD which is beyond day-to-day variability.

Keywords: COPD, acute exacerbations, health-status, day-to-day variability

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by poorly reversible limitation in airflow [1]. COPD is predicted to become the third most frequent cause of death in the world by 2020 [2]. The prevalence of diagnosed COPD is around 350.000 in the Netherlands. This number is expected to be underestimated by under diagnosis of COPD using primary care registrations [3].

The characteristic symptoms of COPD are chronic and progressive dyspnea, cough and sputum production [4], resulting in declination in respiratory function, decreased exercise capacity and a low health-status [5]. Stable day-to-day symptom variability is interrupted by acute exacerbation episodes which vary in severity and frequency both between patients and during the course of one patient's illness [6]. Acute exacerbations of COPD (AECOPD) have been defined as: "a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD" [7]. Another way of defining AECOPD is by using a complex of worsening respiratory symptoms (symptom-based) instead of using respiratory symptoms in combination with an event like the prescription of medication by a family doctor or a hospital admission (event-based) [8]. The number of exacerbations reported in symptom-based studies tend to be higher compared with the number of exacerbations reported in event-based studies. This would suggest that about 50% of real exacerbations would not be reported by a medical professional [9, 10]. Most patients with COPD, experience at least one exacerbation per year [11, 12] which is a significant cause of increased mortality, emergency room visits and higher health care costs [13-15]. AECOPDs might be caused by environmental pollutants (e.g. cigarette smoke) [16], but mostly by respiratory infections [17]. Exacerbations are associated with increased airflow obstruction and can result in a faster decline in lung function [12], increased inflammation [18-20], decreased disease specific quality of life [9] and impaired activity in daily living which do not completely recover when disease comes into remission [21, 22].

Miravittles et al [9] assessed in their prospective cohort study over a two year period the long-term evolution of the health-status of COPD patients. Patients with frequent exacerbations had a 2 units.yr^{-1} worsening of the St George's Respiratory Questionnaire (SGRQ) total score, compared with patients with infrequent exacerbations. Bourbeau et al [23] showed that exacerbations were associated with

statistically significant deterioration in the SGRQ activity and impact domains at exacerbation onset and during the first and second week. The largest improvement of SGRQ score following an exacerbation occurred within the first 4 weeks after exacerbation onset [24]. Although these studies showed that AECOPD had a severe impact on health-status, there was no data available about the day-to-day variations in patients' health-status during stable periods compared to acute exacerbations. This study will increase knowledge of the day-to-day variations of health-status during stable COPD and during the event of an AECOPD. This can be used in developing and evaluating therapeutic interventions aimed at the management of AECOPD in future trials. Primary purpose of this study is to investigate the stable day-to-day variability in health-status of patients suffering from COPD. Secondary aim of this study is to investigate the change in health-status during AECOPD.

METHODS

Study design

In this prospective multi-center cohort study, patients with COPD who agreed to participate in a randomized, controlled trial designed to evaluate the effectiveness of an individualized action plan on recovery of symptom-based quality of life in the event of an exacerbation were selected. For this study only data from patients who received usual care were used (control-group). Ethics approval was obtained from the appropriate ethics review boards.

Study population

Consenting subjects were recruited by respiratory nurses/practice nurse (RN) during scheduled visits between December 2008 and July 2009. All patients gave written consent before enrolment. Patients were selected from primary as well as secondary care units.

Inclusion criteria for this study were the following: 1) Diagnosis of COPD based on the post-bronchodilatator Forced Expiratory Volume in one second (FEV_1) according to the Global Initiative for Chronic Lung Disease (GOLD) standards [4], 2) Diagnosis of COPD as the major functionally limiting disease, 3) Current use of bronchodilatator therapy. Exclusion criteria were: 1) Primary diagnosis of asthma (onset <35 years, > 12% postbronchodilatator reversibility in FEV_1 2) Primary diagnosis of cardiac

disease 3) Primary diagnosis of other functionally limiting disease, that could significantly affect either patients' mortality or participation in the study.

All patients received care as usual which consists of pharmaceutical and non-pharmaceutical care from their general practitioner (GP) and/or respiratory physician (RP) according to most recent evidence based guidelines on COPD care. Patients were consulted at study inclusion by a respiratory nurse (RN) who systematically checked and discussed: vaccination, optimizing medication, inhalation techniques, exercise, nutritional aspects, smoking (cessation) and exacerbation management.

Outcome measures

At baseline sociodemographic data: age, sex and Body Mass Index (BMI) were collected. Medical records were checked for the presence of lung function assessment in the last three months before study inclusion. If this data was not present, lung function measurement was scheduled. Strengthd spirometry following the guidelines (GOLD standards[4]) was used to determine FEV_1 and strengthd vital capacity (FVC). The FEV_1 and FVC results are expressed in percentages of the adult reference of the adult reference values [25].

The SGRQ which produces three domain scores: symptoms, activity and impact and a total score was used to measure health impairment. Its reproducibility and validity have been confirmed [26, 27]. The medical research council (MRC) dyspnea scale was used as a measure of disability [28].

To assure all exacerbations are identified diary cards were used, according to previous studies [29]. All patients were instructed by the researcher to record daily in diary cards if they had worsening of their "major" respiratory symptoms: dyspnea, sputum volume, sputum purulence and if they had worsening of one or more of "minor" symptoms: wheeze, sore throat, cough, running-/congested nose and fever during the past 24 hours (Table 1).

The Clinical COPD Questionnaire (CCQ), a self-administered multidimensional symptom control questionnaire which includes ten items in three domains (symptoms, functional state and mental state), is scored at three day intervals.

Patients were asked to recall their experiences during the last 24 hours and to score this using a 7-point scale from 0 (asymptomatic) to 6 (extremely symptomatic/totally limited). The minimal clinically important difference (MCID) of the CCQ total score is 0.4, determined in a similar study population in terms of age and disease severity

(GOLD Stage) as in the current cohort [30]. The CCQ is valid, reliable and responsive to changes in patients with all stages of COPD [31].

The CCQ and the diary card were combined in a single booklet. After completing one booklet (30 days) patients were asked to return the booklet to the research group. Patients were contacted by telephone after receiving the booklet and the diary cards were discussed to assure if the usage is completely understood. When the last diary card was completed after 24 weeks, patients received a letter where the primary study objectives were revealed.

Exacerbations

Exacerbation diagnosis was based on the symptom score of minor and major symptoms according to Anthonisen et al. [32] (Table 1). Symptom based exacerbations were defined as the onset of two or more new worsening symptoms on two consecutive days with at least one "major" symptom. Exacerbation onset was taken on the first day on which these symptom criteria were met. Minor symptoms were disregarded when identifying exacerbations if they were recorded for more than 5 preceding days before a suspected exacerbation. The reason to exclude these minor symptoms is to avoid identifying exacerbations when patients continuously record the presence of a symptom rather than an increase [29]. According to Hurst et al. exacerbations were categorized into three types: "initial", "relapsed" and "recurrent". The first exacerbation in the study as well as an exacerbation more than 8 weeks after the previous exacerbations is categorized as initial exacerbation. A relapsed exacerbations follows within 5 days and a recurrent exacerbation follows within 8 weeks after a previous exacerbation has ended [33].

Symptom recovery to baseline level was identified using a total daily count of individual symptoms, which was calculated as the sum of the eight symptoms. The presence of a major symptom was scored as normal (0), small increase (1) and a clear increase (2), the minor symptoms were scored as normal (0) or increased (1). Baseline level was determined as the mean total daily symptom count over days -14 to -8 before exacerbation onset. An exacerbation has ended when the three day moving average of symptom count returns to baseline level (Figure 1). The three day moving average was used to minimize the effect of day-to-day variation [34].

All diary cards were independently assessed by two members (DB and BP) of the research team using a list where all exacerbations were reported. Any disagreements

were resolved in a consensus procedure where a third investigator (JT) participated. In case of no consensus the third investigator made the final decision about the exact exacerbation onset and recovery.

After identifying the exacerbations CCQ scores were labeled as CCQ score during stable COPD and CCQ score during AECOPD. There is evidence that over the prodromal period (7 days before onset of exacerbation), dyspnea, symptoms of common cold, sore throat, and cough is increased significant [10]. These changes in the pre-exacerbation period might influence CCQ scores, therefore CCQ scores during the prodromal period (9-1 days before onset of exacerbation) were labeled as "CCQ during the prodromal period".

Statistical analysis

All analysis were performed using Statistical Package for the Social Sciences (SPSS) version 17.0. Kolmogorow-Smirnov test was used to test whether the sample was from a normally distributed population. Normally distributed baseline characteristics were expressed as mean and standard deviation (SD), and skewed data as median and interquartile range (IQR).

The mean exacerbation rate was calculated by pooling all patients in one group and dividing the total number of exacerbations by the total follow-up time. This approach was used to avoid bias for the probability of an exacerbation in a small time interval[35]. Patients' individual CCQ domain and total scores were calculated, missing data were replaced by series mean.

The difference between consecutive CCQ scores (delta) were calculated for all CCQ total and domain scores. All labeled data were pooled and descriptive statistics (mean and standard deviation) were calculated for all CCQ total-, domain scores and deltas.

The independent Students t-test was used to compare mean stable CCQ scores and day-to-day changes between subjects who reported AECOPD during the study period and patients who did not report any exacerbations.

To investigate if there is a statistically meaningful difference between health-status during stable, prodrome and exacerbation period a repeated measures ANOVA, with a Bonferroni correction was used for patients who experienced AECOPD. Mauchly's test of Sphericity was used to indicate that the assumption of sphericity has not been violated.

To investigate the impact of a COPD exacerbation on health-status, two different analyses were performed. The direct impact after exacerbation onset was calculated by comparing the last CCQ score before-, and the first CCQ score after exacerbation onset using a paired-samples t-test. To investigate the maximum impact of a COPD exacerbation on health-status and if this impact is beyond day-to-day variations the maximum CCQ score after exacerbation onset was compared with the mean CCQ score plus one normal standard deviation during stable COPD using a paired-samples t-test.

RESULTS

Patients

Forty patients (22 men and 18 women) met the inclusion criteria and provided informed consent. Nine patients (22.5%) were recruited from primary- and thirty-one patients (77.5%) were recruited from secondary care units. All variables except BMI were normally distributed. The mean age of the study population was 64 years (± 10.5; range: 44-86 years). The mean FEV_1, % predicted was 60.41 (± 18.67). A total of 12.5% of patients were in GOLD [4] stage I, 55% in GOLD stage II, 30% in GOLD stage III, and 2.5% in GOLD stage IV. The average MRC score of the study population was 2.13 (± 1.0).The mean SGRQ scores were: symptoms 60.2 (±26.5), impacts: 24.2 (± 15.3), activity: 48.1 (± 26.9) and the total score was: 48.1 (± 26.9). Baseline characteristics of all 40 patients are summarized in table 2.

Exacerbations

The 40 patients completed daily diary cards for minimal three months (mean 110 ± 27,69 days). There were 28 patients without exacerbation, 4 with one exacerbation and 8 with two or more exacerbations. According to the classification of Hurst [33], 18 of the indentified exacerbations are classified as “initial”, 10 as “recurrent” and 1 as “relapsed” exacerbations. The study population completed daily diary cards for in total 4427 days (12.13 years) and reported 29 exacerbations (rate: 2.39 exacerbations/year).

There were no significant differences in mean stable CCQ domain and total scores between subjects who experienced an AECOPD and subjects who did not report any exacerbations during the study period. Mean day-to-day variations (delta) in CCQ

domain- as well as total scores were significantly higher ($p<0.05$) in the exacerbation group (Table 3), except the domain mental state ($p=0.220$).

Table 4 shows changes in patients' responses to the CCQ during stable COPD, prodrome and AECOPD. Mauchly's test within the ANOVA analysis indicated that the assumption of sphericity had been met. Generally, patients who experienced an AECOPD showed a clinically [30] and statistically significant decrease in their mean health-status compared to stable situations, but this deterioration is not yet present during the prodromal period. This decrease in health status was indicated by patients' responses in mean CCQ total score ($p=0.004$) and the domains symptoms ($p=0.000$) and function ($p=0.009$). There were no statistically significant differences in mean CCQ mental score ($p=0.999$) between stable COPD and AECOPD.

Table 5 shows the CCQ domain and total scores 1-3 days before exacerbation onset and the first CCQ score after exacerbation onset. This table indicates that there is a statistically and clinically [30] significant impact of AECOPD on mean CCQ total scores ($p=0.001$) and its domains symptom ($p=0.000$), function ($p=0.011$) and mental (0.007).

The maximum impact of an AECOPD on health-status is expressed in table 6. It shows the comparison between the CCQ scores when it reached its' maximum after COPD exacerbation onset and the mean CCQ score plus one standard deviation during stable COPD.

This table indicates that there is a clinically [30] and statistically significant decline in health-status during AECOPD which is beyond normal stable day-to-day variations. This declined health-status was expressed in an increased mean CCQ total score ($p=0.000$) and its' domains symptoms ($p=0.000$), functional- ($p=0.000$) and mental state ($p=0.001$).

DISCUSSION

The current study is the first to our knowledge that prospectively determined the day-to-day changes in health-status in stable as well as during an AECOPD. By selecting patients from primary as well as secondary care units the study population is expected to be representative to the source population in terms of age, sex and degree of airflow limitation (GOLD stage [4]). It revealed that there was a clinically [30]

and statistically difference between mean CCQ total, symptom and function scores during stable COPD compared with an AECOPD.

There were no clinically or statistically significant changes in mental state during stable COPD compared with an AECOPD. A possible explanation is that, for some patients, disease exacerbations are a common situation [6] which are not beyond the normal course of their illness. Some patients might have experienced more AECOPDs and might know how to cope with this situation.

Seemungal et al. [10] showed in their study an increase in dyspnea, symptoms of a common cold, sore throat and cough ($p<0.05$) during the prodromal period 7 days before the onset of exacerbation.

In our study there was no difference in heath status during the prodromal stage nine days before exacerbation onset compared with stable COPD or AECOPD. It is likely that this increase of symptoms during the prodromal period reported in the study by Seemungal et al. [10] might have an impact on CCQ symptom scores, however our data did not show any statistically or clinically significant differences. An explanation is that the CCQ in our study was scored on a three day interval, which might have decreased to sensitivity to detect change.

Our secondary purpose was to investigate the impact of an AECOPD on the health-status of patients with COPD. There is no clear definition about what the “impact” of an AECOPD on health-status is, therefore in our study we performed two kinds of analyses. Our first analysis was the direct impact of an AECOPD on health-status, which was the comparison between the last CCQ score before- and the first CCQ score after exacerbation onset. This analysis showed that there is a clinically [30] and statistically deterioration on health-status, as measured with the CCQ and its’ domains ($p<0.05$), directly after COPD exacerbation onset. Bourbeau et al [23] also showed in their study a clinically and statistically worsening of patients’ disease after early identification of an AECOPD. In this study the worsening in health-status was indicated by the responses in CCQ score, the MRC dyspnoea scale and ADL questionnaires.

Our second analysis was performed to investigate the maximum impact of an AECOPD on health-status. This was done by comparing the maximum CCQ score during an exacerbation with the mean CCQ score during stable COPD plus one normal standard deviation. This approach have not been used to our knowledge in past studies and was performed to investigate if the CCQ score during an

exacerbation was beyond normal day-to-day variations. Our study revealed that the maximum CCQ domain and total scores during an AECOPD was clinically and statistically higher compared with stable day-to-day scores ($p<0.001$).

Our study revealed that there was no clinically and statistically difference in mean health-status during stable conditions between patients who had no exacerbations during the study period and patients who had one or more exacerbations. Surprisingly, it showed that the mean day-to-day variations (delta) in health-status during stable COPD was significantly higher in the group who had an AECOPD compared with the group who remained stable. This difference was present in all CCQ total and domain scores except for the domain “mental state”. This might indicate that patients who had an exacerbation have larger day-to-day fluctuations in health-status even during stable COPD.

In the current study we have used a symptom-based definition, where a complex of worsening respiratory symptoms is used to define an acute exacerbation. An advantage of this study is that, by requesting patients to record increases in their daily symptoms, we were able to detect exacerbations which might not be reported by a medical professional [9, 10].

A disadvantage of using daily diary cards is that patients tend to report their daily symptoms rather than an increase of symptoms. Patients had to return their diary cards to the research team each month. Patients were called by a member of the research team to assure it was clearly understood how to use the diary card. Nevertheless some patients maintained reporting daily symptoms rather than an increase of symptoms.

An additional disadvantage of using diary cards is that it was not clear what to do with exacerbations which were started at the beginning of the first diary card. There was no clear endpoint for these exacerbations as they were defined based on the three day moving average, because there was no data available of the daily symptom count (days -14 to -8) before exacerbation onset. The endpoint of these exacerbations was defined in the consensus procedure and was mostly based on decreased symptom count and day-to-day symptoms reported in continuous diary cards. Nevertheless this might have caused biased results.

In this study we have estimated the exacerbation rate by dividing the total number of exacerbations by the total duration of person-time of follow-up of the group. This weighted approach produces the correct and best estimate of the exacerbation rate

[35]. A limitation of the current study is the relatively short follow-up period (mean 3.7 months), where most patients with COPD experience at least one exacerbation per year [11, 12]. The follow-up time might not be long enough to assure that an exacerbation could have occurred. This might have biased outcomes, because patients could have falsely been labeled as patients without any exacerbations rather than patients with exacerbations in stable condition.

Past studies have revealed that patients with COPD with frequent exacerbations had a worsening of their health-status on the long term, compared with patients with infrequent exacerbations [9, 36]. Our study is the first to our knowledge which was able to detect day-to-day variations in health-status during stable COPD and AECOPDs. In conclusion AECOPDs in patients with COPD are associated with a clinically and statistically deterioration in health-status. Decrease in health-status during an AECOPD outreaches the bandwidth of normal day-to-day variations in stable periods.

Table 1: Major and minor symptoms according to Anthonisen et al. [32]

Major symptoms	**Minor symptoms**
Dyspnea	Wheeze,
Sputum volume	Sore throat
Sputum purulence	Cough
	Running-/congested nose
	Fever during the past 24 hours.

Table 2: Baseline characteristics of study patients (n=40)

Male gender, %	55 (n=22)
Age (years)	64 ± 10.5
Weight (kg)	79.2 ± 17.6
Height (cm)	173.1 ± 8.2
BMI (kg/m²)	Median: 26.33 (IQR: 22-30)
MRC	2.13 ± 1.0
Pulmonary function test	
FEV_1 (l)	1.74 ± 0.67
FEV_1 (% predicted)	60.41 ± 18.67
FVC (l)	3.42 ± 0.87
FVC (% predicted)	96.08 ± 18.25
FEV/ FVC	48.92 ± 12.82
FEV/FVC (% predicted)	0.63 ± 0.16
GOLD stage	2.23 ± 0.71
SGRQ	
Total	48.1 ± 26.9
Symptoms	60.2 ± 26.5
Impacts	24.2 ± 15.3
Activity	48.1 ± 26.9

Table 3: CCQ domain and total scores, patients with and without an AECOPD

Characteristics	No exacerbation (n=28)	Exacerbation (n=12)*	p-value
Symptom score			
Mean	2.16 (0.46)	2.29 (0.55)	0.729
Delta	0.21 (0.33)	0.38 (0.45)	0.001
Function score			
Mean	2.10 (0.36)	2.08 (0.48)	0.966
Delta	0.19 (0.26)	0.33 (0.41)	0.003
Mental score			
Mean	0.84 (0.33)	1.09 (0.27)	0.261
Delta	0.17 (0.30)	0.18 (0.28)	0.220
Total score			
Mean	1.81 (0.29)	1.97 (0.39)	0.691
Delta	0.14 (0.20)	0.28 (0.31)	0.003

Values are expressed as mean (SD); * CCQ scores during stable COPD

Table 4: CCQ scores during stable, prodrome and exacerbations

Characteristics	Stable	Prodrome	Exacerbation	F-ratio*	p-value**
Symptom score	2.29 (0.55)	2.58 (0.62)	3.32 (0.75)	15.38	0.000
Function score	2.08 (0.48)	2.40 (0.47)	2.95 (0.63)	8.02	0.009
Mental score	1.09 (0.27)	0.81 (0.48)	1.16 (0.63)	2.14	0.999
Total score	1.97 (0.39)	2.16 (0.38)	2.73 (0.56)	10.34	0.004

Values are expressed as mean (SD); *Sphericity assumed: ** p-value comparison between stable COPD and AECOPD

Table 5: Impact of an AECOPD after onset

Characteristics	CCQ score before AECOPD (days -3 to -1)	CCQ score after exacerbation onset (0-2 days)	%>MCID	p-value
Symptom score	2.77 (1.22)	3.91 (0.96)	79.2	0.000
Function score	2.50 (1.34)	3.43 (1.25)	62.5	0.011
Mental score	0.68 (0.84)	1.10 (1.23)	37.5	0.007
Total score	2.24 (1.06)	3.12 (0.95)	62.5	0.001

Values are expressed as mean (SD)

Table 6: Maximum impact of an AECOPD on health-status

Characteristics	Mean CCQ + one standard deviation*	Maximum CCQ score during exacerbation	%>MCID	p-value
Symptom score	3.05 (1.24)	4.64 (0.98)	91.6	0.000
Function score	2.64 (1.15)	4.11 (1.29)	66.7	0.000
Mental score	1.04 (1.26)	1.84 (1.57)	50.0	0.001
Total score	2.42 (1.04	3.65 (0.92)	75.0	0.000

Values are expressed as mean (SD); * CCQ scores during stable COPD

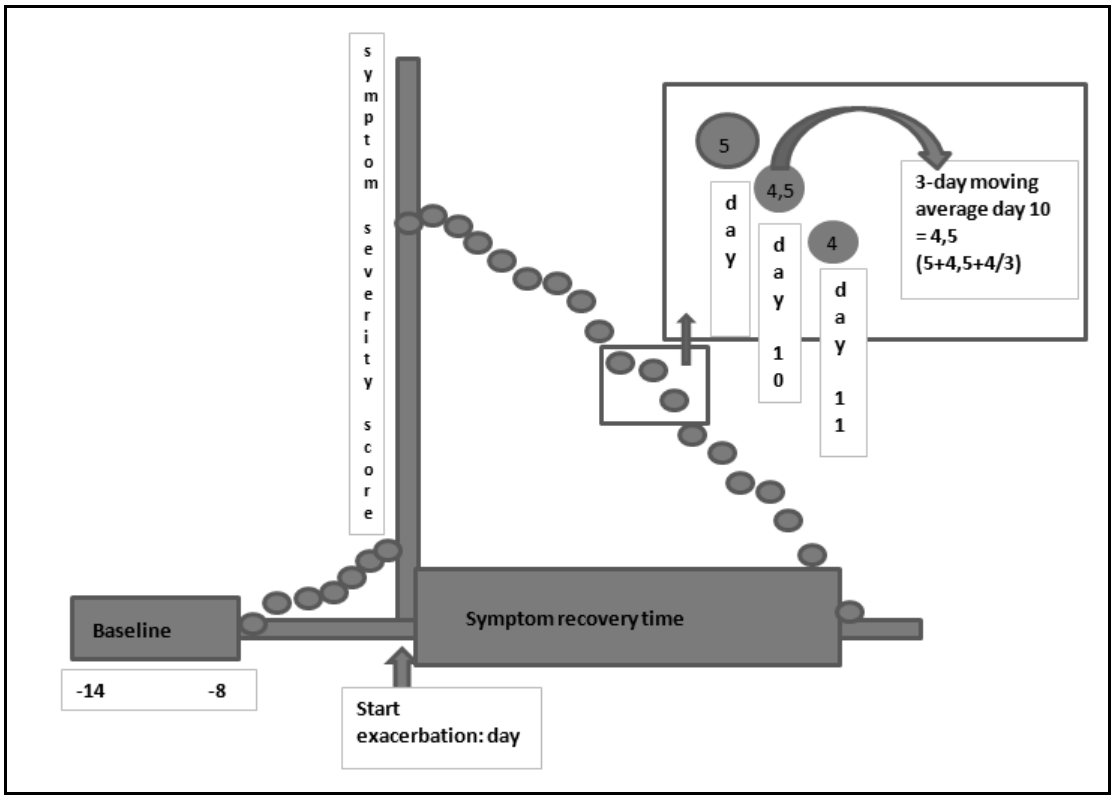

Figure 1: Baseline and 3-day moving average

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