Decline of Health Status Sub-Domains by Exacerbations of Chronic Obstructive Pulmonary Disease: A Prospective Survey

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Key Words

Chronic obstructive pulmonary disease • Exacerbations • Health status

Abstract

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are held responsible for a decline in health status (HS). This may not apply equally to all exacerbations, because different definitions are required for quite different illnesses. Selection of definitions and the sensitivity of the HS instrument may affect results regarding the impact of exacerbations. Sensitivity of a new HS instrument, which covers different and more aspects, has not yet been tested, with respect to exacerbations. **Objectives:** Confirmation of the negative HS effect of exacerbations by using a highly differentiated instrument, and to evaluate which aspects of HS are affected most. **Methods:** One hundred and sixty-eight ambulatory patients with COPD were evaluated prospectively with regard to a wide range of HS aspects, at the beginning and end of a 1-year follow-up. Recording of symptom changes and treatment on monthly diary cards resulted in the identification of event-based exacerbations. HS was assessed via a newly validated instrument integrating both physiological and non-physiological sub-domains. Parametric correlations were calculated between exacerbation fre-

quency and HS scores at the end of the study. Partial correlations were then explored using HS scores at baseline to correct for prior HS levels. **Results:** Correlations between exacerbation frequency and HS sub-domains were found to be frequent, predominantly in non-physiological sub-domains. After correction for HS scores at baseline, only 2 sub-domains (belonging to the main domain 'Complaints') remained significantly but weakly correlated. **Conclusion:** Exacerbation frequency and HS show weak correlations after a year, but most of these disappear after correction for prior HS levels. In such exacerbations, aggravated HS probably takes much longer to manifest itself.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a condition which has documented effects on several health aspects, namely ventilatory reserve, mortality, hospital admission rate and health-related quality of life (HRQL). Apart from these parameters, exacerbations have been studied in the last two decades as an additional outcome measure. They form a distinct aspect in the individual burden of COPD, require a great deal of expense in medical care and influence hard end points. Furthermore,

they are considered to impose, on their own, a negative effect on health status (HS) [1–6]. Although the short-term effects are particularly striking, negative effects in the long term have also been reported. Such effects seem to occur more commonly in frequent exacerbators [3, 7, 8].

Because exacerbations of COPD are defined by highly variable criteria with subsequent variation in severity of their course and thus outcome, their effects may vary along with their definition. Clearly, those identified by the necessity for hospital admission are those most likely to cause deterioration in HS, demonstrated by high rates of 1-year mortality after hospital admission for exacerbations [9, 10]. Recently, a large survey of COPD admissions in the UK revealed that severity of exacerbations based upon unexpected radiological infiltrates may affect prognosis also in terms other than mortality [11, 12]. In ambulatory patients for whom a course of corticosteroids and/or antibiotics is sufficient treatment for the exacerbations [5, 8, 13], the evidence also supports such a deleterious role, albeit with a less hazardous outcome. Both types of exacerbation are considered to be so-called event-based exacerbations, that affecting ambulatory patients occurring more frequently than that associated with in-hospital treatment. When a symptom-based definition is used, less convincing reports are seen with respect to HS deterioration [6, 7]. In fact, an improvement in the St. George's Respiratory Questionnaire (SGRQ) scores was noted over a 2-year period, with less improvement in frequent exacerbators.

There is as much variation in methods for assessment of HS as there is in the definitions of COPD exacerbations. Establishing a relationship of HS with exacerbations may suffer from this lack of standardization. Several instruments are available, but a gold standard cannot be assigned. Nearly all of them encompass only some aspects of HS, since HS is defined as an overall concept incorporating physiological functioning, symptoms, functional impairment and quality of life (including HRQL) as main domains [14, 15]. Most instruments meant to measure HS do not account for all these domains. In this study, we use a detailed assessment of HS, covering 4 main domains and consisting of 16 sub-domains, providing more complete assessment [16]. We evaluated the magnitude of the effects on HS of those exacerbations seen most frequently in daily practice. A prospective cohort of ambulatory patients was followed up for 1 year, measuring HS at the beginning and the end of the study. With these follow-up data, we examined whether a change in HS scores was attributable to exacerbation frequency. The event-based definition for ambulatory patients was chosen because of the high prevalence of that

type of exacerbation and a relatively objective means of establishing this. We postulated that, at least, some HS aspects would be negatively affected by exacerbations.

Methods

Design of Study

A longitudinal cohort of patients with COPD was followed for 1 year. They were recruited from 3 different outpatient departments in urban and suburban areas. Patients received the usual care from these medical centres with regular control visits in ambulatory wards. They all underwent a detailed assessment of their pulmonary function and other aspects of HS, according to the Nijmegen Integral Assessment Framework (NIAF) [16], both at baseline and after follow-up. Cardio-pulmonary exercise testing was conducted only at assessment 1. Exacerbations were monitored each month over the 1-year period.

Patients

For this study, 168 eligible ambulatory patients with moderate and severe COPD – mostly GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage II–III – were included after written informed consent and formed the patient sample at baseline. Twelve patients ultimately ended up with GOLD stages I ($n = 4$) or IV ($n = 8$) based on their lung function measurement at baseline, in contrast to prior pulmonary function in the recruitment phase. The study was approved by the ethics committee of the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands. For detailed information about the recruitment procedure, see Vercoulen et al. [16]. In summary, inclusion followed if: an established diagnosis of COPD was made within GOLD stages II and III ($FEV_1/FVC < 70\%$ and $30\% < FEV_1 < 80\%$ predicted after bronchodilation), and they were in a stable clinical condition without exacerbation in the 6 weeks prior to enrolment and they had not participated in a pulmonary rehabilitation program within the previous 6 months.

Exclusion followed if patients had important comorbidity that could interfere with the study protocol or evaluation of HS components, likely to be influenced by such conditions as cardiac, neurological or oncological disease and diabetes.

Exacerbations

Once a month over the 1-year follow-up period, patients completed structured diary cards, and returned these by mail each time. They recorded fatigue and breathlessness, and whether a change of cough, sputum production, sputum colour and dyspnoea had occurred compared to their normal stable state – for at least 3 days consecutively in the preceding month. In addition, extra doses of bronchodilating inhaler therapy and courses of antibiotics and/or prednisone, administered by their general practitioner or chest physician, had to be recorded. Furthermore, some questions regarding medical consultations including hospital admission had to be answered. The diary card contained 17 questions in total. During follow-up, patients were urged not to visit the clinic for any confirmation or treatment of their exacerbations, other than regular visits and in line with usual care policy. Patients who completed and returned 10 or more diary cards were considered evaluable.

Table 1. List of physiological measurements and questionnaires used in the NIAF and its specific relation to each sub-domain

Parameters		
Physiological functioning		
Airflow	FEV ₁ %, MEF 50%, VE %	
Hyperinflation	TLC %, RV %	
Exercise capacity	VO ₂ %, TLCO %, Δ BE, HR _{max} %	
Gas exchange	Δ (A-a) DO ₂	
	Δ PaCO ₂	
Muscle force	PI _{max} %, PE _{max} %, leg force %	
Body composition	BMI and FFMI	
Instrument		Subscale
Complaints		
Subjective pulmonary complaints	Physical Activity rating scale - dyspnoea	global activities global burden specific activities
Dyspnoea emotions	Dyspnoea Emotions questionnaire Quality of Life for Respiratory Illness questionnaire Dyspnoea Emotions questionnaire	dyspnoea subjective breathing problems frustration mood anxiety
Expected dyspnoea fatigue	Physical Activity rating scale - dyspnoea Fatigue checklist individual strength	expected dyspnoea subjective fatigue
Functional impairments		
Actual physical activity	accelerometer	
Behavioural impairments	sickness impact profile	body care and movements home management mobility ambulation
Subjective impairments	Quality of Life for Respiratory Illness questionnaire experienced burden of daily activities global impairment sickness impact profile	general activities social activities total total burden social interaction
Quality of life		
General	Satisfaction with Life scale symptom checklist Beck Depression Inventory	total anxiety primary care
Satisfaction health	Satisfaction with Life scale	satisfaction-physical satisfaction-future
Satisfaction relations	Satisfaction with Life scale	satisfaction-spouse satisfaction-social
Δ (A-a) DO ₂ = Change in alveolar-arterial oxygen difference during cycle exercise test; Δ BE = change in base excess during maximal cycle exercise test; FFMI = fat-free mass index; HR _{max} % = maximum heart rate as percentage of predicted; MEF = maximum expiratory flow; PE _{max} % = maximal expiratory mouth pressure percentage predicted; PI _{max} % = maximal inspiratory mouth pressure percentage predicted; VE % = minute ventilation at maximum exercise in percentage predicted; VO ₂ % = maximal oxygen consumption as percentage of predicted.		

Table 2. Patient characteristics at baseline, comparing those included (complete follow-up measurements and ≥ 10 diary cards) and excluded from analyses (drop-outs or incomplete diary cards)

	Total sample (n = 168)	Included in analyses (n = 116)	Excluded from analyses (n = 52)
Age, years	64.5 (9.1)	64.4 (9.4)	64.6 (8.6)
Sex M/F	131/37	92/24	39/13
Married (n = 163)	129 (79.1)	95 (82.6)	34 (70.8)
Smoking history (n = 166)	(n = 166)	(n = 115)	(n = 51)
Current	45 (27.1)	23 (20.0)	22 (43.1)
Ex-smoker	98 (59.0)	78 (67.8)	20 (39.2)
Non-smoker	23 (13.9)	14 (12.2)	9 (17.7)
Duration of COPD diagnosis (n = 161)			
<1 year	20	16	4
1–10 years	64	45	19
>10 years	77	53	24
IVC, litres	3.6 (0.90)	3.7 (0.86)	3.5 (1.0)
IVC %pred.	92.7 (15.5)	90.6 (15.6)	93.6 (15.4)
FEV ₁ p.b., litres	1.52 (.48)	1.56 (.48)	1.42 (.48)
FEV ₁ %pred.	51.6 (13.6)	52.8 (14.1)	48.8 (12.1)
FEV ₁ /IVC, %	42.9 (11.3)	43.5 (11.7)	41.9 (10.5)
TLC (%pred.)	103.1 (16.0)	103.6 (16.3)	101.9 (15.6)
TLCO (%pred.)	68.7 (23.9)	69.9 (24.6)	66.1 (22.0)
PaO ₂ , kPa	10.9 (1.4)	10.9 (1.2)	11.0 (1.7)
PaCO ₂ , kPa	5.2 (0.5)	5.1 (0.5)	5.2 (0.6)
BMI	25.6 (4.1)	25.9 (4.1)	24.8 (3.9)
PI _{max} (%pred.)	114.0 (34.2)	114.6 (33.0)	112.5 (37.2)

Data presented as mean (SD), or frequency (%). IVC = Inspiratory vital capacity; FEV₁ p.b. = forced expiratory volume in 1 s after bronchodilation; FEV₁ %pred. = FEV₁ as % predicted; FEV₁/IVC % = FEV₁ as percentage of IVC; TLC = total lung capacity; TLCO = transfer factor of lung for carbon monoxide; PI_{max} = maximal inspiratory mouth pressure.

Table 3. Frequency distribution of exacerbations in 116 evaluable patients with total and mean number, according to GOLD stage

Exacerbation frequency ^a	GOLD stage distribution				Total (%)	Number of exacerbations
	I	II	III	IV		
0	0	24	10	1	35 (30.2)	Total ^b : 257 Mean/patient: 2.20
1	0	18	7	1	26 (22.4)	
2	1	9	6	1	17 (14.7)	
3	1	7	8	3	19 (16.4)	
≥ 4	1	8	9	1	19 (16.4)	
Total	3	66	40	7		

^a In patients who completed ≥ 10 diary cards.

^b In the study sample during the 12-month follow-up.

From the cards, the frequencies of exacerbations per patient were identified. We selected an event-based definition, based on the sole criterion of use of an antibiotic and/or a course of prednisone for increases in symptom severity.

Health Status Measurement

HS was assessed by the NIAF developed by our research group [16]. This provides a validated clinical assessment that includes physiological as well as non-physiological aspects. It warrants a detailed assessment of HS, covering Physiological Functioning, Complaints, Functional Impairments and Quality of Life as main domains. These four main domains were subdivided into 16 relatively independent sub-domains [16, 17], each representing a unique aspect of HS. Each sub-domain is represented by a single score, the Sub-Domain Total Score (STS). Table 1 shows detailed information regarding the description of main domains, sub-domains and their constituting of instruments as a result of the data handling by the NIAF.

Statistics

Basic analyses were performed to evaluate demographic characteristics and the clinical and physiological data of the sample. Total number, range and means of exacerbation frequency were calculated.

Exacerbation frequency taken as a continuous variable was correlated with the HS STS at follow-up by Pearson correlations. To evaluate whether causal relationships exist between exacerbations and HS, partial correlations were calculated between exacerbation frequency and HS at follow-up, controlling for HS at baseline. p values were set at 0.05.

Results

Patient Characteristics

Patient characteristics are presented in table 2. After recruitment, 168 patients were included, mainly older men, a majority of whom had a clear smoking history and had had a diagnosis of COPD for years. They represented moderate-to-severe COPD according to GOLD criteria, with mean BMI just above the upper limit of normal, signs of mild hyperinflation and diminished diffusing capacity for carbon monoxide. Mean values of partial pressure of oxygen and of carbon dioxide in arterial blood (PaO₂ and PaCO₂) were within normal limits. Mean inspiratory muscle strength was slightly above normal.

Figure 1 shows details of the inclusion of patients and the subsequent number of dropouts (n = 22). Ultimately, 116 patients proved evaluable with regard to baseline data and the follow-up registration of exacerbations. The frequency distribution of exacerbations is listed in table 3, together with the distribution of GOLD stages. Due to missing data concerning HS at assessment 2, another 9 patients were excluded from follow-up analyses after a year, leaving 107 individuals for studying. Sequelae of the

Fig. 1. Flow chart of inclusion of patients with subsequent follow-up events, numbers of participants and reasons for drop-out.

sample showed a death rate at 1 year of 2.9%. Hospitalization because of exacerbations occurred in 17 of 116 patients with complete data (14.6%).

Effect of Exacerbation Frequency on Health Status

Correlations between exacerbation frequency and HS sub-domains (STS) showed 8 of 15 sub-domains to be significant (table 4). Though 1 sub-domain in a main domain, Physiological Functioning, was significant, the non-physiological domains predominately represented the significant correlations; however, correlations were weak in every sub-domain.

To account for the effects of the prior HS condition, partial correlations were analyzed. Only 2 sub-domains were significantly correlated with exacerbation frequen-

cy, but very weakly (table 4). Both were components of a main domain, Complaints: Subjective Pulmonary Complaints and Expected Dyspnoea.

Discussion

Main Results of the Study

This study showed that the HS effects of exacerbations in ambulatory patients are hardly detectable after 1 year of follow-up. To a large extent, the positive correlations between exacerbation frequency and HS at a certain moment in the course of COPD proved to be accounted for by prior HS condition. This was the case for nearly all HS sub-domains.

Table 4. Correlations between exacerbation frequency and HS sub-domains (STS) measured after follow-up with partial correlations in the right column, involving correlations with baseline HS (STS baseline)

Main domain with sub-domain differentiation	Pearson	Partial correlation
Physiological functioning		
Airflow	0.161	0.178
Hyperinflation	-0.121	-0.1
Exercise capacity ^a	0.233*	0.154
Muscle force	0.036	-0.048
Body composition	0.091	0.063
Complaints		
Subjective pulmonary complaints	0.292**	0.207*
Dyspnoea emotions	0.186	0.123
Expected dyspnoea	0.258**	0.267**
Fatigue	0.234*	0.112
Functional impairments		
Actual physical activity	0.076	0.088
Behavioural impairments	0.238*	0.094
Subjective impairments	0.315**	0.11
Quality of life		
General	0.273**	0.091
Satisfaction health	0.196*	0.069
Satisfaction relations	0.13	0.127

Correlations and partial correlations. Here, it is only based on TLCO %pred measured at follow-up.

* $p < 0.05$ and ** $p < 0.01$.

^a This refers to cycle ergometry conducted at baseline, composed of HR_{max} %pred., VO_{2max} %pred., TLCO %pred. and Δ BE. See footnotes to tables 1 and 2 for explanation of abbreviations.

Effects of Exacerbations on Subsequent Health Status

Associations of exacerbation frequency and subsequent HS were similar to the results of earlier reports [1, 4, 5]. It is not clear from the literature whether all exacerbations cause HS impairment. This is because there is such variety in the design and methodology of studies, besides varying definitions of exacerbations and variability in the assessment of HS itself. It is only with regard to its strong association with mortality that there seems to be little doubt, provided in-hospital exacerbations are taken into account. However, it is obvious that many patients suffer episodes of exacerbation long before they reach terminal illness. How these exacerbations relate to HS derangements is less clear. Available reports show some evidence that HS declines with exacerbation frequency, but HS was measured either shortly after exacerbations [4, 18] or by retrospective means [13, 19, 20]. Long-term studies with prospective design have delivered only indirect or weak evidence for a harmful effect on HS (by demonstrat-

ing slower recovery months after an exacerbation in those with a second exacerbation) [4, 6, 7]. These studies recruited ambulatory patients in general. Another study, which has often been cited and also provides some evidence [8], represents a post hoc analysis, dealing with the effect of inhaled corticosteroids upon HRQL. It claims that the corticosteroids exert a protective effect on SGRQ scores by lowering exacerbation frequency.

The exacerbations in our sample of ambulatory patients can be considered to represent average severity. They are defined by physician-based clinical diagnosis calling for outpatient medical treatment. Only a small number necessitated hospital admission and, moreover, 1-year mortality was low, indicating that they did not represent the most severe exacerbations, and can thus be regarded as being in between 'very mild' and 'more severe' exacerbations. Care was taken to avoid the effects of short-term changes in HS by excluding patients with recent exacerbations.

By taking into account the prior levels of HS represented by the scores at the start of follow-up, the possible influence of these variables was eliminated by calculating partial correlations. This statistical method provides a correction of already existing correlations a priori and makes the true causal role of exacerbations more visible. In doing so, it in fact appears that in none of the 16 sub-domains was a clear effect of foregoing exacerbations detectable. The correlations of Dyspnoea Expected and Subjective Pulmonary Complaints are of such small magnitude that we are left no other interpretation. Hence, the conclusion can be drawn that HS is not affected by moderately severe event-based exacerbations in ambulatory patients after a 1-year period. This is against our postulate, but not in true contrast to studies of Llor and Miravittles et al. [6, 7]. For they showed that, primarily based on symptom-based exacerbations, SGRQ scores actually improved in both groups of exacerbators, the infrequent as well as the frequent. Interestingly, the frequent exacerbators had higher, i.e. worse, HRQL scores already from the outset, which fits in with findings of significant correlations of HS sub-domains with exacerbation frequency upon entering our study. It also seems to counter the data reported by Spencer et al. [8], which estimated a decline in SGRQ total score of somewhere around 2.4–2.9 units over a 3-year period. Such a rate, however, means that there was no clinically relevant change (a minimum of 4 points), and so a decline, if present, can be considered minimal.

In summary, this study further delineates the existing evidence regarding the causal role of exacerbations in the decline of HS. Depending on severity and the pre-exist-

ing level of HS, within a limited time span of several years, in mild-to-moderate exacerbations the effects may be nearly absent.

Perspective

Overlooking the studies mentioned above, it seems clear that the effects of exacerbations on HS are differentiated. The severity of the exacerbations plays an important role in the ultimate effects. It is also evident that the definition of exacerbations used for any particular study will influence severity to a large extent, confounding the results. How can all the different evidence be put together in perspective?

Evidence so far seems to reveal that symptom-based exacerbations – presumably mild exacerbations, since about half of them remain unreported and thus untreated [1] – have no detectable impact on HS within a 2- to 3-year time span. If not too frequent, they might even show better HS after some time for as of yet unclear reasons, which could be hidden in a bias caused by participating in a long-term study. Event-based exacerbations, which rely upon diagnoses via the involvement of a physician, may have no or only a minor impact on HS, if treated predominantly outside of the hospital. HS aspect scores may fluctuate strongly depending on the interval between exacerbation onset and the moment of measurement. In the long run, extending this by at least 6 months, frequent exacerbaters may not fully recover, resulting in a slow worsening of certain HS sub-domains. This process appears to take several years to develop. Earlier and probably more prominent changes in HS may occur in patients who have been admitted for an exacerbation who receive appropriate treatment in hospital wards. They might show an accelerated decline of HS.

Strength and Weaknesses

This study is credited by its longitudinal design with considerable length, 2 consecutive assessments and the use of a well-validated and detailed assessment of HS. We are aware of only 3 studies with a comparable or longer follow-up [1, 6, 7]. Some reports which state that exacerbation frequency is associated with decline in HS, are cross-sectional or they measured HS only at the end of follow-up [1, 13]. The chosen method for assessment of HS (NIAF) has some advantage over HS instruments with a longer tradition, such as the SGRQ and the CRQ (Chronic Respiratory Disease Questionnaire). Most instruments measure only a few aspects of HS and do not always measure the aspect of HS that they were thought to measure [21]. The NIAF aims to cover all relevant as-

pects of HS [16], and, therefore, is a convenient tool when looking into detail which aspects of HS are affected by exacerbations.

The exclusion of patients with recent exacerbations renders a relative independency of short-term effects on HS sub-domains. Within 6 weeks, most symptoms of an exacerbation have subsided, promoting the evaluation of long-term effects [22, 23]. On the other hand, a 1-year follow-up may be too short to develop changes in HS great enough to become significant. Longer follow-up studies, however, are more difficult to perform because of the increasing number of dropouts or incomplete data. Besides, the mean frequency of exacerbations in this study (2.2) is similar to rates in studies of comparable length, and thus seems adequate in exerting an effect.

Another relative weakness is that we used monthly diary cards to identify event-based exacerbations by self-reporting. Medical records were not checked as to whether oral courses of antibiotics and/or prednisone had indeed been given.

Implications

This study, once more, demonstrates the concern with the wide variety of events captured by the term exacerbation. It appears that HS decline by home-treated exacerbations over a time span of 1– to 2 years is minimal (sub-clinical) at most. That is why, above all, further studies are required with a particular effort to define exacerbations and their severity as clearly as possible. They could then be directed into more binding variables with regard to their consequences, than variables with elementary labels like frequency, as it is now. Studies with a long follow-up are envisaged for moderately severe and mild exacerbations, in order for effects to be detected.

The repeated finding of clear associations of low HS with exacerbation frequency also requires further study, because we do not know how this intricate relationship comes about. It cannot be excluded that both phenomena mutually reinforce each other. It seems worth exploring the notion of low HS being a risk factor for developing exacerbations, in order to obtain the tools to intervene and prevent the exacerbations. As an example, depression has been shown to be a factor that predicts exacerbations [24].

Limitations

The patient sub-population in this study contained patients with only minor comorbidities. The exclusion of major comorbidity might have changed the correlations

between HS sub-domains and exacerbation frequencies, with respect to their impact on HS. Comorbidity is likely associated independently with disability and age, and may affect the trend to introduce medical care, thereby indirectly altering the frequency of exacerbations [13, 20, 25]. Extrapolation of the results to other subpopulations of COPD cannot therefore be made.

Conclusion

Exacerbations of COPD, more specifically the ones considered moderately severe and occurring in the majority of ambulatory patients, do not exert a measurable

effect on HS as measured by the NIAF in a 1-year follow-up. The negative effect of this type of exacerbation on HS is apparently a slowly developing phenomenon.

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