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Title: Objective measurement of cough frequency during COPD exacerbation convalescence

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Abstract

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Cough and sputum production are associated with adverse outcomes in COPD and are common during COPD exacerbation (AE-COPD). This study of objective cough monitoring using the Hull Automated Cough Counter and Leicester Cough Monitor software confirms that this system has the ability to detect a significant decrease in cough frequency during AE-COPD convalescence. The ability to detect clinically meaningful change indicates a potential role in home monitoring of COPD patients.

Key Words: COPD, Cough, Exacerbation, Outpatient Monitoring, Telehealth.

Introduction

Chronic obstructive pulmonary disease (COPD) represents a significant public health problem worldwide and results in disabling progressive symptoms with episodes of rapid worsening termed acute exacerbations (AE-COPD) [1].

COPD is characterised by persistent airflow obstruction, however, reliance on spirometric measures alone fails to capture the marked heterogeneity of symptomatology and prognosis [2]. Whilst the recent GOLD guidelines [3] have partially addressed this there is a pressing need to improve COPD characterisation.

Cough and sputum production are reported by 60-80% of COPD patients [4,5] yet physicians significantly under appreciate the importance of these symptoms to a patient's wellbeing [6]. Chronic cough and mucus hypersecretion in COPD are associated with accelerated lung function decline, more frequent exacerbations and earlier mortality [7-9].

AE-COPD cause significant morbidity and mortality. Cough and shortness of breath are cardinal features of AE-COPD [10] and worsen in the prodrome [11]. Monitoring cough frequency therefore has potential applications in both the phenotyping and identification of AE-COPD. We report a longitudinal, observational study of objective cough monitoring over 45 days during AE-COPD convalescence.

Methods

Subjects with COPD who were admitted to hospital with an AE-COPD (defined by increased cough and one or more of breathlessness, increased sputum volume or sputum purulence)

were included in the study. The study was approved by the local research ethics committee (LREC number 11/NW/0643).

Subjects underwent 24-hour cough monitoring using a hybrid system consisting of the Hull Automated Cough Counter (HACC) and Leicester Cough Monitor (LCM) software on days 1, 5, 20 and 45 following hospital discharge. The HACC is an ambulatory device that continuously records audio in mp3 format. Audio files were analysed using the validated, semi-automated LCM software (Leicester, United Kingdom) generating an hourly cough count and summary of cough events [12]. Subjects also performed home FEV-1 monitoring using a hand held spirometer (Vitalograph, Cambridge, United Kingdom) and completed the COPD Assessment Test (CAT), Leicester Cough Questionnaire (LCQ), and Hull Airways Reflux Questionnaire (HARQ).

Because cough monitoring during AE-COPD convalescence has not previously been studied, validation was performed to determine the sensitivity, specificity, and positive and negative predictive values of the HACC/LCM system. The LCM software cough count was expressed in cough seconds (the number of seconds during which there was a cough) and compared with aurally determined cough count during 3 hours of audio recordings in each subject at two time points (day-time and night-time) on day 1 following hospital discharge. To assess consistency in sensitivity within individuals, this was repeated in selected patients on day 45.

Results

18 subjects completed the study (mean±SD age: 68.1±7.3 years; FEV1: 0.99±0.53 L/min; male: 44%; current/ex-smoker: 39%/61%) with a total of 72 monitored days. Complete cough monitoring data were available for 63/72 monitored days (87.5%) and completed questionnaires were available for 67/72 monitored days (93%). Home FEV1 data were

available for only 21/72 monitored days (29.2%). The most common reason for failure of home FEV1 monitoring was subjects failing to undertake the procedure.

Cough frequency (coughs per hour) significantly decreased during AE-COPD convalescence (figure 1). The cough frequency during the day was significantly greater than at night (P=0.02) but day and night cough frequencies strongly correlated (Day 1: r = 0.66, P <0.01. Day 5: r = 0.87, P<0.01. Day 20: r = 0.73, P<0.01. Day 45: r = 0.97, P<0.01).

The LCQ (higher scores indicate better cough related quality of life) and HARQ scores improved significantly during the study (mean±SEM LCQ: Day 1, 10.5±1.0; Day 5, 12.8±0.8; Day 20, 13.6±1.3; Day 45, 14.8±1.1, P=0.02. HARQ: Day 1, 44.1±3.4; Day 5, 37.9±3.3; Day 20, 29.1±4.0; Day 45, 29.6±3.9. P=0.01). There was a trend towards improvement in CAT scores but this did not reach statistical significance (Day 1, mean±SEM 26.6±2.0; Day 5, 23.5±2.2; Day 20, 20.9±2.6; Day 45, 20.5±2.9).

Objective cough frequency moderately correlated with all three subjective measures of respiratory symptoms (LCQ, HARQ and CAT) but was unrelated to home FEV1 measurement (table 1 and figure 2).

	Correlation with Cough Frequency	
	r	**p**
LCQ	- 0.44	<0.01
HARQ	0.59	<0.01
CAT	0.52	<0.01
FEV1	- 0.12	0.43

Table 1. Correlation between mean cough frequency per hour over 24 hours, home FEV1 measurement and subjective measures of respiratory symptoms (CAT, HARQ and LCQ).

During validation, the overall sensitivity of objective cough counting using the HACC/LCM system was 57.9% with a specificity of 98.2%. This translated to a positive predictive value of 80.9% and negative predictive value of 94.6%. Unsurprisingly, there was interpatient variability in objective cough detection sensitivity, however for individual patients, sensitivity was strongly correlated between day 1 and day 45 ($r=0.93$, $P=0.007$).

Discussion

We provide objective evidence that cough frequency falls significantly during the convalescent period following an AE-COPD. This supports previous subjective reports that cough significantly increases prior to AE-COPD and returns to baseline following treatment [11]. Decline in cough frequency was most marked within the first five days in keeping with reports of subjective symptom profiles in AE-COPD [11] but a reducing trend continued up to day 45 reflecting a prolonged recovery phase.

In keeping with previous reports, we demonstrate only moderate correlation between objective and subjective measures of cough frequency suggesting that these metrics reflect different facets of the clinical picture [13-15].

The mean sensitivity of the HACC/LCM cough monitoring system in this study is lower than previously reported in stable patients using the LCM [12]. This may reflect a more challenging acoustic environment during AECOPD or it could be due to the hybrid nature of HACC/LCM system with the LCM software not specifically optimised to operate with the HACC. However, the sensitivity of the HACC/LCM system is largely consistent in the same individual at different time points. Since this error is consistent we suggest it can detect change in cough frequency

within an individual over time and therefore detect trends. Monitoring trends in biometric data forms the basis of telemonitoring (remote patient monitoring). Ambulatory cough counting may be an important metric to enhance the value of COPD telemonitoring.

There are a number of challenges to the routine use of home monitoring in COPD patients. Current methods use daily patient symptom reporting and monitoring of basic physiological parameters including pulse oximetry and heart rate. However there is no evidence that the current methodology offers the ability to detect and undertake a timely intervention in the event of clinical deterioration. A variable that can be measured passively and increases in the prodrome of an AE-COPD might be the key. We demonstrate that objective cough monitoring, unlike many other measures, can identify important change in clinical state. Whether this is true in clinical practice requires further testing. The passive nature of cough monitoring also adds to its attraction for home monitoring. In contrast spirometry, an active, patient dependent observation was poorly complied with by our patients. Additionally, objective passive monitoring has the advantage of overcoming the risk of fatigue that can develop from completing daily questionnaires. Finally, another potential advantage of cough monitoring is identification of patients with an unrecognised chronic cough phenotype, thus guiding diagnosis leading to alternative interventions and allowing the assessment of response.

This study has a number of limitations. The sample size is relatively small and although adequately powered to demonstrate a decline in cough frequency following AE-COPD it only included patients requiring hospitalisation and therefore we cannot draw conclusions about patients with community managed exacerbations. One of the diagnostic criteria used for AE-COPD was increase in cough and we may thus be selecting against patients without this as a

prominent symptom. The utility of cough monitoring in AE-COPD without cough remains untested.

We provide the first objective evidence that cough frequency decreases during AE-COPD convalescence and demonstrate that objective cough monitoring is sensitive to clinically meaningful change. A large prospective study of daily objective cough monitoring in COPD patients is warranted to explore its potential role in home monitoring.

Figure Legends

1. Cough frequency (coughs per hour) on days 1, 5, 20 and 45 following hospital discharge with an acute exacerbation of COPD.

2. Correlation between cough frequency and CAT score (a) HARQ score (b) LCQ score (c) and home FEV1 measurement (d).

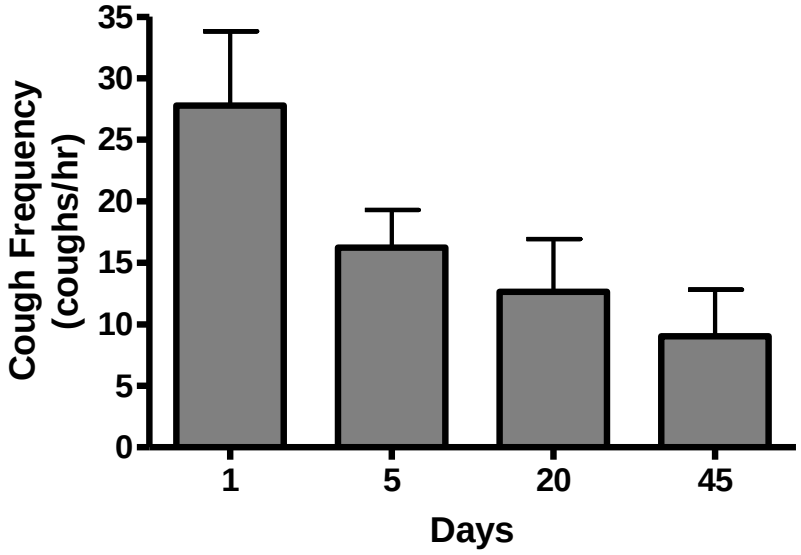

Figure 1

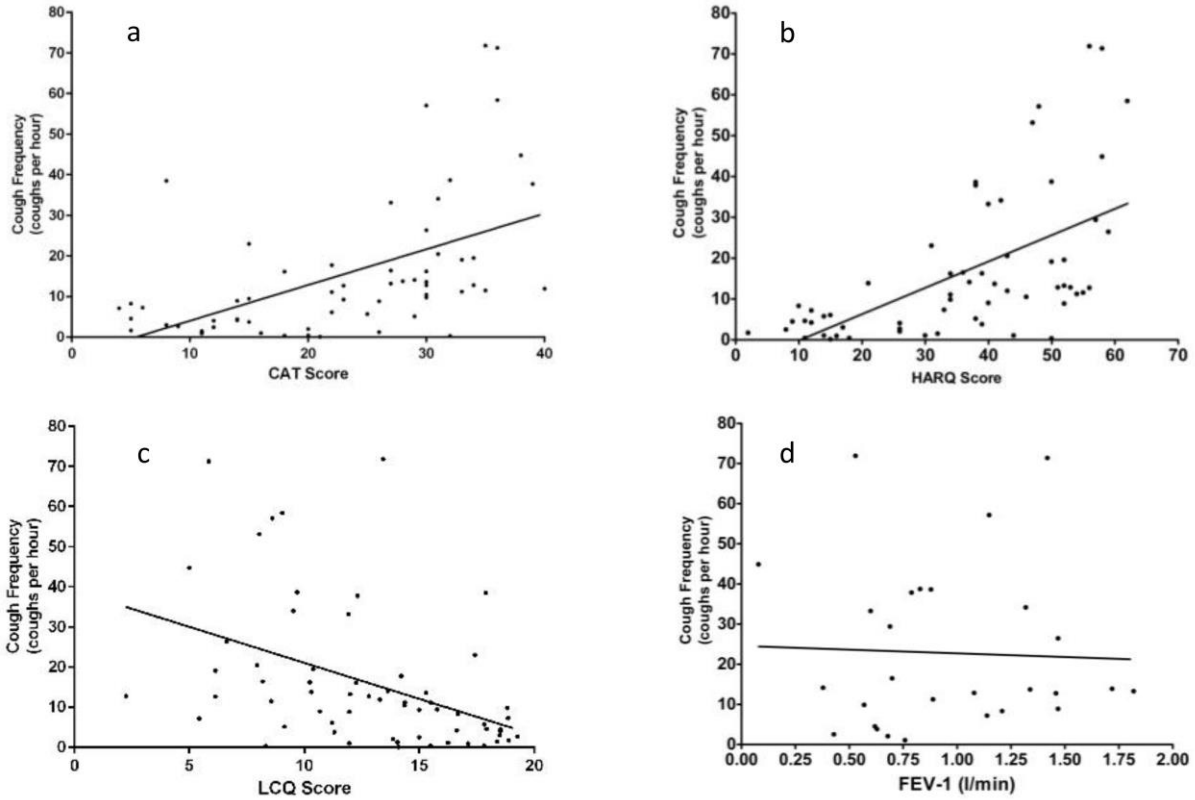

Figure 2

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Conflicts of Interest: This study was part funded by Philips.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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