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Validation of the Leicester Cough Monitor (LCM): preliminary findings using an automated cough detection system in patients with chronic cough

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ABSTRACT

Chronic cough is a common condition that presents to both primary and secondary care. Assessment and management are hampered by the absence of well-validated outcome measures. We present the validation of the Leicester Cough Monitor (LCM), an automated sound based ambulatory cough monitor.

We measured cough frequency with the LCM and compared it to coughs and other sounds counted manually over 2 hours of a 6-hour recording by two observers in 9 patients with chronic cough to determine the sensitivity and specificity. Automated cough frequency was also compared to manual counts from one observer in 15 patients with chronic cough and 8 healthy subjects. All subjects had 6-hour recordings. A subgroup of 6 normals and 5 patients with a stable chronic cough had repeat automated measurements at least 3 months apart. A further 50 patients with chronic cough had 24-hour automated cough monitoring.

The LCM had a sensitivity and specificity of 91% and 99% for detecting cough and a false positive rate of 2.5 events/hour. Mean (SEM) automated cough counts/hour were 48(9) in patients with chronic cough and 2(1) in normals (mean difference 46; 95% confidence interval 20 to 71; $p<0.001$). The automated cough counts were repeatable (within subject standard deviation 11 coughs/hour; intraclass correlation coefficient 0.9; $p=0.001$). The cough frequency in patients undergoing 24-hour automated monitoring was 19 coughs/hour; day-time (8am-10 pm) cough frequency was significantly greater than overnight cough frequency (25 vs 10 coughs/hr; mean difference 15, 95% confidence interval of difference 8 to 22; $p<0.001$).

The LCM is a valid and reliable tool that can be used to assess 24-hour cough frequency in patients with cough. It should be a useful tool to assess patients with cough in clinical trials and longitudinal studies.

INTRODUCTION

Chronic cough is a common reason for referral to respiratory physicians. The assessment of patients with chronic cough is commonly based on the anatomical, diagnostic protocol which is a systematic evaluation based on the understanding that most cases are due to disease of the upper respiratory tract where cough receptors are most plentiful.[1] The most common conditions implicated in causing chronic cough in non-smokers are asthma, gastro-oesophageal reflux and rhinitis or a combination of these.[2]

The identification of an important contribution by these conditions is largely based on the evaluation of treatment trials.[3] However, there are few well-validated outcome measures to assess cough severity and treatment efficacy. Cough visual analogue scores, diary score cards, quality of life questionnaires, cough reflex sensitivity measurement and cough monitors have been proposed as potential tools to assess cough severity.[2] The subjective nature of symptom scores and quality of life questionnaires[4,5] and the poor specificity of cough reflex sensitivity measurement[6] to identify patients with chronic cough have led to a renewed interest in the development of automated ambulatory cough monitors.[7-15] We have previously shown that there are marked differences in cough frequency between patients with chronic cough and healthy subjects, that these measurements are repeatable and have suggested that cough frequency measurement is potentially useful in the assessment of patients with chronic cough.[7] Currently available cough monitors are limited by difficulty achieving unrestricted ambulatory measurement in the patients' own environment, the inability to perform 24-hour recording and the lack of automated cough detection systems. We set out to develop an automated cough monitor (Leicester Cough Monitor: LCM) capable of recording cough sounds for 24 hours. We present our validation of the monitor and preliminary findings of six- and 24-hour recordings in patients with chronic cough.

METHODS

Subjects

Fifteen consecutive patients with an isolated chronic cough (>3 weeks duration) were recruited from a specialised cough clinic. The clinic receives referrals from primary and secondary care largely confined to a population of 970,000 within Leicestershire. The causes of cough in patients with chronic cough were: cough variant asthma (n=4), gastro-oesophageal reflux (3), eosinophilic bronchitis (1), idiopathic (3), post-viral (1), bronchiectasis (1), chronic obstructive pulmonary disease (1) and chronic bronchitis (1). Nine of these patients were randomly selected for the first stage of validation (cough variant asthma (n=4), eosinophilic bronchitis (1), idiopathic (2), post-viral (1), bronchiectasis (1)) and all patients were included in the second validation stage. Investigations were carried out according to a standardised algorithm.[16] The protocol for investigation and treatment, and criteria for accepting diagnosis were as previously described.[16] Eight normal controls were recruited from healthy volunteers responding to local advertising. Normal subjects were asymptomatic, non-smokers and had normal spirometry and a methacholine PC_{20} FEV_1 >16mg/ml. No patients had received corticosteroids or other specific treatment for the condition causing cough for at least six weeks prior to the study. A randomly selected subgroup of six healthy subjects and 5 patients with a stable chronic cough and treatment requirements (3 with cough variant asthma, 1 with gastro-oesophageal reflux associated cough and 1 with idiopathic chronic cough) participated in cough frequency repeatability studies three to six months after the first, at the same time of day in order to avoid possible bias from diurnal variations. Fifty further consecutive patients with chronic cough were recruited to evaluate 24-hour recordings with the Leicester Cough Monitor (idiopathic cough (26), asthma (8), eosinophilic bronchitis (2), rhinitis (2), sarcoidosis (2), gastro-oesophageal reflux (3), bronchiectasis (2), chronic obstructive

pulmonary disease (2), enlarged tonsils (2) and obstructive sleep apnoea (1)). All subjects gave full informed written consent to participate. The protocol for this study was approved by the Leicestershire Research Ethics Committee.

Cough Monitor

The Leicester Cough Monitor (LCM; patent pending) is a digital ambulatory cough monitor that records sound continuously from a free field microphone necklace (Sennheiser MKE 2-5, Sennheiser electronic GmbH & Co. KG, Wedemark, Germany) onto a MPEG audio layer-3 (MP3) recorder at a sampling frequency of 16 kHz and with an encoding bit rate of 64 kbps (iRiver iFP-799, dimensions 26.7x87x32mm, iRiver Europe GmbH, Eschborn, Germany; Figure 1). The cough monitor was attached at 9am in all subjects and returned 6-24 hours later. Subjects were told that the LCM was a new investigative tool being developed to assess the nature of the cough and were encouraged to resume their normal activity in their usual environment. Data stored on the recorder was downloaded onto a computer when the recording was complete where it was analysed by an automated cough detection algorithm (Leicester Cough Algorithm; patent pending).

A general outline of the Leicester Cough Algorithm has been described previously.[8] Briefly, the detection algorithm is based on Hidden Markov Models, a statistical method that can be used to characterise the spectral properties of a time-varying pattern. We implemented the cough detection algorithm based on the keyword-spotting approach, as defined in speech recognition, in which the objective is to detect the occurrence of a particular set of keywords in a sequence of continuous speech. Continuous ambulatory recordings in patients with chronic cough were used to train statistical models of the characteristics of cough sounds and of the audio background**.** During the detection process, the recorded audio signal is divided

into contiguous 10-second segments to be analysed by the Hidden Markov Models based algorithm. Each 10-second audio segment is recognised by the detection algorithm as a sequence of variable-length audio sections, each of them classified either as background audio or as a possible cough sound, depending on its statistics.[8] A second algorithm phase then uses brief operator input to facilitate the automated algorithm to eliminate sounds that might have been wrongly classified as cough events in this first phase. For this, the operator is asked to classify based on audio, as cough or otherwise, a small fraction of the sounds detected in the first phase as possible cough sounds (this phase takes 5 minutes to do for a 24-hour recording; approximately 50 sounds are classified). The algorithm then uses this information to create statistical models that are adapted to the characteristics of the cough sounds for that particular recording, and uses these models to classify the remaining sounds that were not shown to the operator.

Cough was defined as a characteristic explosive sound. The algorithm identifies coughs as single events whether they occur as isolated events or in a cluster i.e. attempts were made to determine how many coughs occurred in paroxysms.

Validation

Stage 1

The first stage of validation compared automated cough counts against those identified by manual sound analysis of the first and fourth recorded hours of nine randomly selected patients with chronic cough. Manual analysis of sound recordings consisted of three blinded observer counts (observer 1 twice and observer 2); a cough and non-cough sounds were positively identified when all three observers were in agreement based on sound and visual inspection of the acoustic trace. Each cough sound was identified separately whether

occurring singly or in a cluster or 'epoch' of coughs. Intra and inter-observer variability in cough counts was established from the two blinded analyses of the 1st and 4th hours done by observer one, and by comparing the mean of observer 1's counts for these periods with counts obtained by observer 2. The recordings were analysed twice by the Leicester Cough Algorithm to assess within recording repeatability. In order to classify non-cough sounds and determine whether particular sounds were wrongly classified by the automated system, the first observer listened to all 6-hours of these 9 nine patients and classified all recognisable sounds. Results of this analysis was compared to the automated classification.

Stage 2

The second stage of validation was extended to all recordings and compared automated cough counts against coughs identified manually by observer 1 who analysed the entire 6-hour recording. A further 50 patients with chronic cough underwent 24-hour automated cough frequency measurement. Automated cough frequency was compared for repeatability studies.

Analysis

Subject characteristics were described using descriptive statistics and expressed as means (standard error) for parametric data and medians for non-parametric data. Cough frequency was expressed as individual coughs per hour for the duration of the recording. The validity of the Leicester Cough Monitor was presented as sensitivity, specificity and false positive rate of the automated algorithm for detecting coughs as measured by observer manual analysis. Intra- and inter-observer variability of manual cough counts and repeatability data was assessed as intraclass correlation coefficients and within subject standard deviation.

RESULTS

The subject characteristics are as shown (table 1).

Validation stage 1 (First and fourth recorded hour)

Mean cough counts were 39 coughs/patient/hour by automated analysis compared with 43 coughs/patient/hour by manual analysis (mean difference -4; 95% confidence interval of difference –6 to 13; p=0.4). The intra and inter-observer intraclass correlation coefficients for manual analysis of sound recordings (between observer 1 and 2) were 0.99 and 0.98 respectively (both $p<0.001$). The intraclass correlation coefficient for the repeatability of automated cough analysis for the same recording was 0.99; $p<0.001$. The intraclass correlation coefficient between automated and the manual observer counts was 0.9, $p<0.001$ (figure 2a). The accuracy of manual and automated coughs appeared similar in recordings containing paroxysms and those with isolated coughs. The Leicester Cough Algorithm had sensitivity and specificity of 91% and 99% respectively for detecting cough sounds and a median false positive rate of 2.5 events/patient/hour against the gold standard of coughs detected manually by observer 1 twice and observer 2. There was no evidence that any particular sound was more likely to be classified as a false positive (figure 3).

Validation stage 2 (Six-hour recordings)

Mean (SEM) automated cough counts/patient/hour were 48(9) in patients with chronic cough and 2(1) in normals (mean difference 46; 95% confidence interval 20 to 71; $p<0.001$; figure 4). There were no significant differences in cough frequency between diagnostic groups. The cough analysis took 2 hours to complete, comprising of 5 minutes for data download, 1 hour 45 minutes for computer automated analysis (phase 1: operator not required to be present) and 10 minutes for operator input (phase 2) and printing results.

The intraclass correlation coefficient between automated and observer counts was 0.93, $p<0.001$ (figure 2b). The Leicester Cough Algorithm had sensitivity and specificity of 86% and 99% respectively for detecting cough sounds and a median false positive rate of 1.0 events/patient/hour.

The automated cough counts were repeatable in the 11 subjects that underwent repeatability testing (within subject SD: 11.4 coughs/patient/hour; intraclass correlation coefficient 0.9; p=-0.001; figure 5). The cough frequency in patients undergoing 24-hour monitoring was 19 coughs/patient/hour; day-time (8am-10 pm) cough frequency was significantly greater than overnight cough frequency (25 vs 10 coughs/patient/hr; mean difference 15; 95% confidence interval of difference 8 to 22; $p<0.001$; figure 6).

DISCUSSION

The LCM is a lightweight 24-hour automated ambulatory cough monitor that is easy to use and measures cough in the subjects' own environment. We have shown that it is a valid and reliable tool for objectively measuring cough frequency. The high sensitivity and specificity for the detection of cough sounds is comparable to other routine diagnostic clinical tools and superior to that reported for other more cumbersome cough detection systems. We present preliminary data showing that cough frequency measured with the LCM is repeatable over at least 3 months, a period which is relevant to the duration of treatment trials which form an important part of the assessment of patients with chronic cough. Repeatability was marginally better than recordings analysed manually.[7] Our data suggests that the LCM might be a particularly useful outcome measure in assessing patients with cough and measuring the response to therapy in the clinic and in clinical trials.

A limitation of our study is that evaluation of cough frequency was based on 6-hour daytime cough recordings because at the start of the research battery life was limited to 6-8 hours. Advances in battery technology since then have allowed us to extend recordings to at least 24 hours. The automated system has allowed these recordings to be counted relatively quickly and accurately; it should facilitate the investigation of potential diurnal variations in cough frequency and the effects of potential cough aggravants such as environmental pollution, cigarette smoking and gastro-oesophageal reflux. Our study suggests that a range of sounds including speech, throat clearing and environmental noises caused false positives detected coughs; there was little evidence that any of these sounds caused particular difficulties with detection nor did cough paroxysms appear to present problems for accurate manual and automated cough counts. However, greater experience with the monitor may identify sounds or cough paroxysms that present particular problems for the algorithm to classify and allow

further refinement of the algorithm. Our study involved small numbers and it will be important to study a larger population of normal controls and patients with well defined respiratory disease before and after treatment and subjects studied in different environments to fully validate the cough monitor. This preliminary work suggests that such a study will be feasible.

We were able to achieve 24-hour recordings when advances in battery life made this possible. Cough frequency was stable through the day and was significantly reduced overnight compared to daytime in keeping with previous data suggesting a diurnal variation in cough frequency.[5,9,13] Further work is required to determine the validity and the short and longer-term repeatability of 24 hour cough recordings.

A limitation of this study is that only two hours per recording were used to compare automated cough counts with those obtained from manual counting for the validation study. Manual cough counting is very time consuming and laborious so the first and fourth hours of each recording were counted for consistency. Each recording was manually counted three times to obtain a more robust measure of the true cough frequency. The LCM had a high sensitivity and specificity for detecting cough against this gold standard. This was confirmed in the second part of the validation study where cough counts derived from automated analysis of six-hour recordings were compared with cough counts derived from a single manual observer. The sensitivity of the cough algorithm was slightly lower with six-hour recordings compared with two-hour recordings. This is most likely due to a more robust measure of true cough frequency used for the two-hour recordings compared with single observer manual counts used for the six-hour recordings.

A potential criticism of cough counts derived from audio recordings is that they might not accurately reflect the true cough rate since it is not possible to visualise the act of coughing. However, a recent study compared manual cough counts from audio with video recordings and found them to be very similar.[17] This study concluded that manual cough counts from audio recordings should be regarded as the gold standard to validate cough monitors since audio recordings had superior sound quality to detect cough compared with that from video recordings.

The LCM quantifies cough frequency as single episodes of cough rather than epochs or clusters of coughs and cough seconds (seconds containing cough) used by others.[12] We feel that single cough episodes are a more meaningful measure and easier to interpret by physicians and patients. We chose to measure cough frequency rather than intensity since cough events are less influenced by microphone position and muffling of sounds by covering the mouth during the act of coughing. Furthermore, cough intensity determined by sound analysis lacks responsiveness compared to cough frequency in clinical trials of antitussive drugs.[10] Cough intensity determined by other parameters such as airflow or chest wall movement is less practical for routine clinical measurement. The LCM was validated in subjects with chronic cough due to a wide range of conditions so it reliably detects coughs with differing characteristics.

One of the challenges of developing cough monitors in the past has been differentiating cough sounds from throat clearing, sneezing, speech and other cough-like sounds. The LCM differentiates cough form other sounds reliably as indicated by the high sensitivity and particularly high specificity for detecting cough. The LCM represents a potential advance over existing cough monitors in that it is portable outside a controlled environment, it does

not require measurement of abdominal EMG and it can be set to record for 24-hours. The 24-hour sound recording is discarded after the automated analysis process thereby ensuring patient privacy. The LCM could be used to validate the presence of excess cough, to assess cough severity and to objectively evaluate response to therapy. Further studies are required to assess the use of the LCM in clinical practice.

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OBTAINING THE LEICESTER COUGH MONIITOR

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Table 1. Subject characteristics.

Data expressed as mean (SEM); FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

	Normal	**Chronic cough**
Number (male)	8 (0)	15 (5)
Age (years)	48 (3)	55 (4)
Cough duration (years)	-	5 (2)
FEV_1 %predicted	91 (5)	89 (7)
FEV_1/FVC (%)	79 (1)	75 (4)

FIGURE LEGENDS

Figure 1.

Leicester Cough Monitor

Figure 1. Leicester Cough Monitor

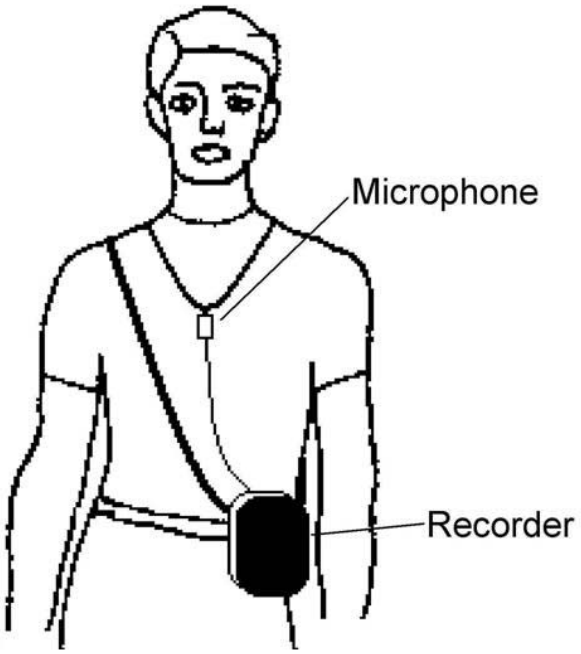

Figure 2.

Bland-Altman plot of automated vs manual observer cough counts/patient/hour.

a) Validation stage 1: First and fourth recorded hour (n=9). Each hour is depicted individually.
b) Validation stage 2: Six-hour recordings (n=23).

The complete cough detection algorithm (phases 1 and 2) was tested in each validation stage. Solid line represents mean difference and dashed line represents 95% limits of agreement (2 x within subject standard deviation). Open symbols: normals; closed symbols: chronic cough.

Figure 2. Bland-Altman plot of automated vs observer cough counts/patient/hour.
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(b) Validation stage 2: Six-hour recordings (n=23).
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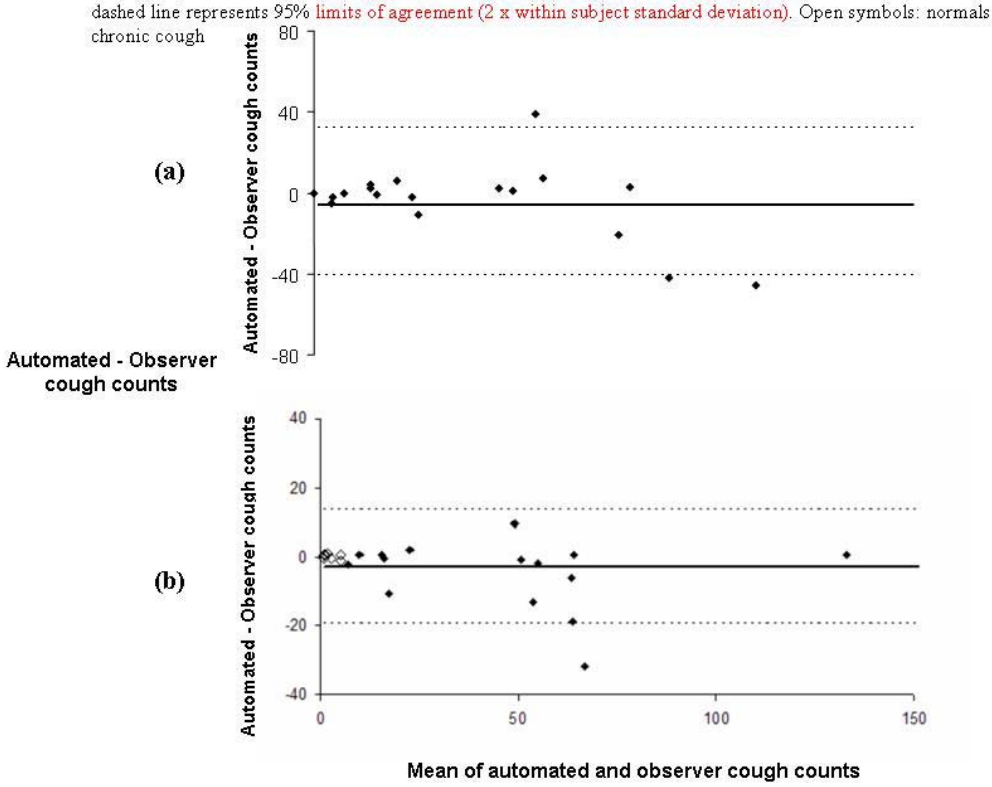

Figure 3.

False positives characterised manually that were detected by the automated Leicester Cough Monitor in nine 6-hour recordings of patients with chronic cough.

Automated detection consists of 2 phases: phase 1: automated analysis of sound recording. phase 2: automated analysis after operator input.

The sensitivity for cough detection in this analysis is slightly lower than that from the gold standard validation stage 1 since the comparator was a six-hour manual counting by observer 1 only.

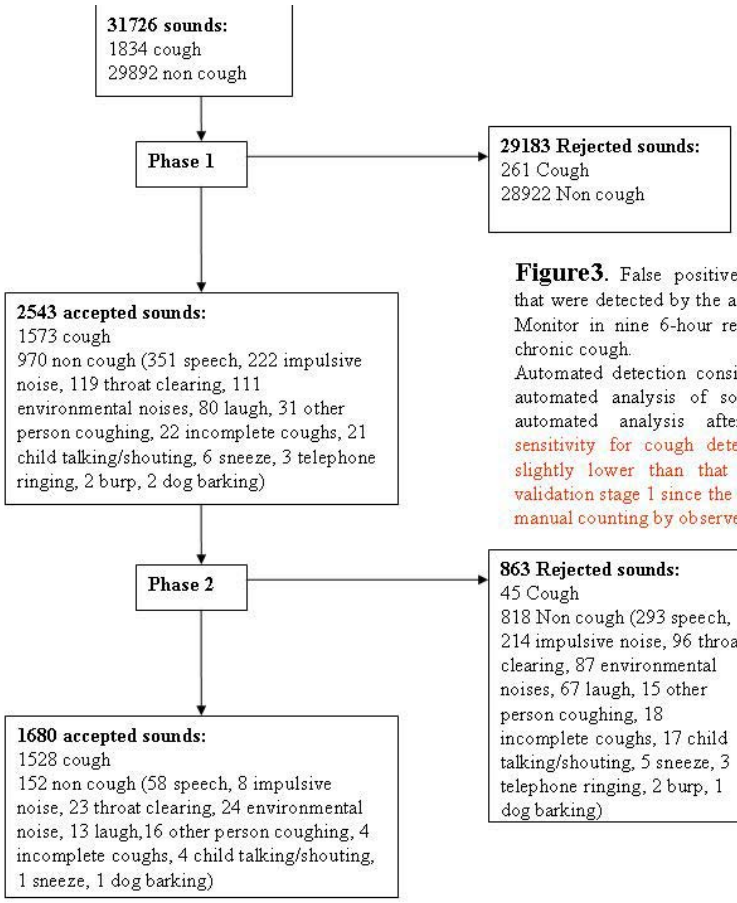

Figure3. False positives characterised manually that were detected by the automated Leicester Cough Monitor in nine 6-hour recordings of patients with chronic cough.
Automated detection consists of 2 phases: phase 1: automated analysis of sound recording. phase 2: automated analysis after operator input. The sensitivity for cough detection in this analysis is slightly lower than that from the gold standard validation stage 1 since the comparator was a six-hour manual counting by observer 1 only.

Figure 4.

Mean (SEM) automated cough counts/patient/hour in healthy controls and patients with chronic cough (6-hour recordings).

Figure 4. Mean (SEM) automated cough counts/patient/hour in healthy controls and patients with chronic cough (6-hour recordings).

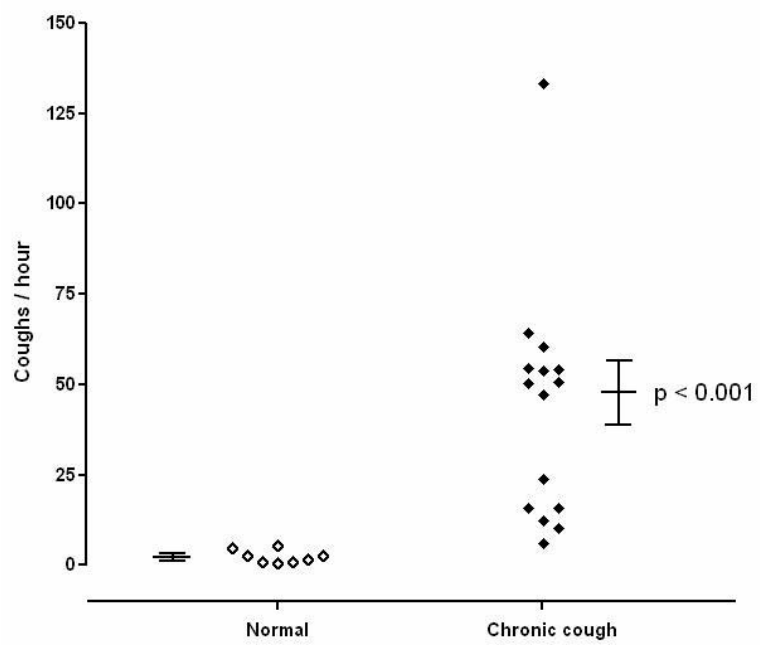

Figure 5.

Bland-Altman plot of automated cough counts/patient/hour repeated over 3-6 months in patients with chronic cough and healthy subjects.

Solid line represents mean difference and dashed line represents 95% limits of agreement (2 x within subject standard deviation). Open symbols: normals; closed symbols: chronic cough.

Figure 5. Bland-Altman plot of automated cough counts/patient/hour repeated over 3-6 months in patients with chronic cough and healthy subjects.
Solid line represents mean difference and dashed line represents 95% limits of agreement (2 x within standard deviation). Open symbols: normals; closed symbols: chronic cough.

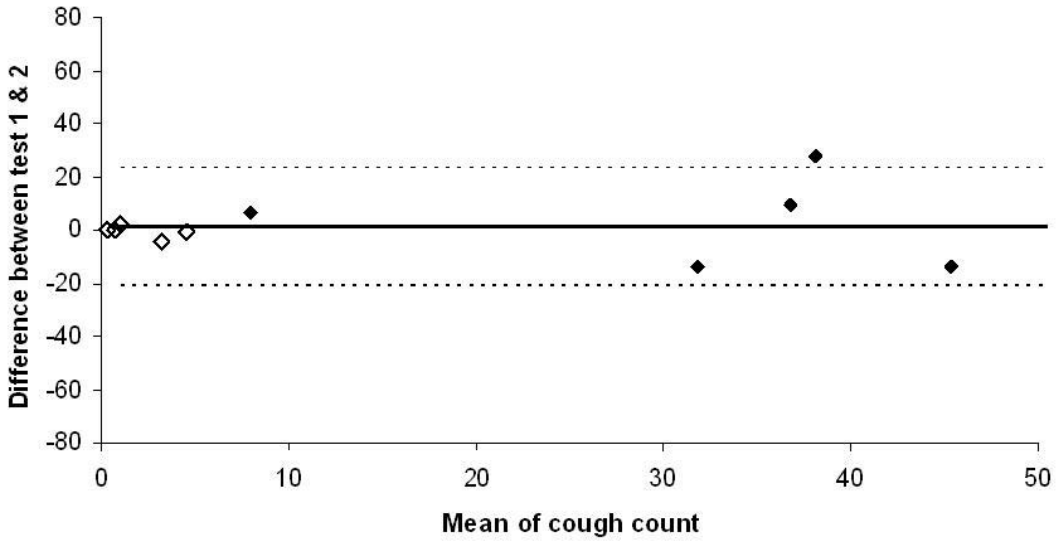

Figure 6.

24-Hour ambulatory, automated cough frequency recordings in 50 patients with chronic cough.

Bars represent mean (SEM) number of coughs/patient.

Figure 6. 24-Hour ambulatory cough frequency recordings in 50 patients with chronic cough. Bars represent mean (SEM) number of coughs/patient.