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Cough frequency in health and disease

To the Editor:

Chronic cough is a difficult clinical problem, partly because there is an absence of well-validated means to assess cough [1, 2]. We have previously reported that the semi-automated computerised Leicester Cough Monitor detects cough accurately over 6 h and that cough frequency is increased in patients with chronic cough compared to controls [3, 4]. There remains uncertainty on the performance of the system over 24 h and across the range of expected cough frequency in larger populations. We set out to address these questions in healthy adult volunteers and adult volunteers with respiratory disease.

44 healthy volunteers were recruited from those responding to a poster advertisement. All reported no current respiratory symptoms, were nonsmokers with a <5 pack-yr past smoking history and had normal spirometric values, methacholine airway responsiveness and induced sputum inflammatory cell counts. 78 patients with respiratory disease were recruited from respiratory clinics. The diagnostic criteria for the conditions have been described previously [5]. Six current smokers and four males taking angiotensin converting enzyme inhibitors (ACEi) were also recruited. The study was approved by the Leicestershire, Northampton and Rutland Research Ethics Committee.

All volunteers underwent spirometry and those with normal spirometry had a methacholine inhalation test using the tidal breathing method. The Leicester Cough Monitor (iRiver iFP-799 mp3 device; iRiver Europe GmbH, Eschborn, Germany and Sennheiser MKE 2–5 field microphone; Sennheiser electronic GmbH & Co. KG, Wedemark, Germany) was attached and recordings obtained and analysed as previously described [6].

The validity of the Leicester cough algorithm was assessed by randomly selecting 20 recordings (eight healthy volunteers, 12 patients with respiratory disease) which were analysed manually [3] by a blinded observer and then by the Leicester cough algorithm. The patients with respiratory disease had the following diagnoses: unexplained chronic cough (n=6), asthma (n=3), eosinophilic bronchitis (n=2) and chronic obstructive pulmonary disease (n=1). A capsaicin cough challenge was performed after removal of the cough monitor [5]. Sputum was induced and processed as described previously [7]. Patients with respiratory diseases completed the Leicester Cough Questionnaire (LCQ) [8]. Patients also completed a 100-mm cough Visual Analogue Score (VAS) [3].

Coughs per 24 h, C2 and C5 (concentration of capsaicin required to elicit two and five coughs, respectively) were log normally distributed and were log transformed prior to analysis. An unpaired t-test was used to compare means between groups. Agreement was assessed by the intra-class correlation coefficient. Correlations between variables were analysed using the Pearson correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-parametric data. Statistical analysis was performed using SPSS (version 16; SPSS Inc., Chicago, IL, USA).

The geometric mean (log$_{SD}$) manual and Leicester cough algorithm counts per 24 h in 12 patients with conditions associated with cough and eight healthy volunteers was 467 (0.32) *versus* 446 (0.32) and 16 (0.7) *versus* 22 (0.4), respectively. There was stronger agreement as assessed by the intra-class correlation coefficient between manual and counts in patients (0.98) than in healthy volunteers (0.85). The sensitivity and specificity, respectively, of the automated system was 83.8% and 99.9% in patients and 82.3% and 99.9% in healthy volunteers.

In the total population of healthy adults the geometric mean (log$_{SD}$) number of coughs per 24 h was 18.6 (0.5). Females coughed more than males (geometric mean (SD) 29.5 (0.4) *versus* 8.3 (0.5); mean difference 3.5-fold; 95% CI 1.9–6.8; $p<0.001$). There was no correlation between 24-h cough frequency and C2 ($r= -0.08$) or C5 ($r= -0.03$). Daytime cough counts (08:00–22:00 h) were higher than night-time cough counts and hourly cough frequency tended to be higher in early morning and mid-afternoon. Cough frequency was not related to body mass index ($r=0.08$) or age ($r=0.12$).

In the total population of adults with respiratory disease the geometric mean (log$_{SD}$) number of coughs per 24 h detected using the automated system was 275 (0.37) (15.8-fold; 95% CI 9.7–21.9; $p<0.001$) greater than healthy controls. Geometric mean (log$_{SD}$) cough frequency C2 and C5, and the mean$\pm$SD cough VAS and LCQ score by group are shown in table 1. Females coughed more than males (geometric mean (log$_{SD}$) 381 (0.43) *versus* 198 (0.4); mean difference 1.9-fold; 95% CI 1.1–3.2; $p=0.012$). Cough frequency was not different from normal in the six current smokers (table 1) but was higher in the four males taking ACEi compared to healthy males (geometric mean (log$_{SD}$) 128 (0.2) *versus* 8.3 (0.5); mean fold difference 15.7-fold; 95% CI 4.2–58.7; $p<0.001$). There was a significant correlation between the 24-h cough frequency and the cough VAS ($r=0.66$, $p<0.001$), C2 ($r= -0.35$, $p<0.001$), C5 ($r= -0.5$, $p<0.001$) and the LCQ ($r= -0.44$, $p=0.001$). In the group with respiratory disease the cough frequency by hour followed a similar pattern to that seen in healthy controls and there was no difference in the diurnal pattern of coughs by disease. In all subjects log cough frequency was significantly associated with sputum neutrophil count ($r=0.36$, $p<0.0001$) and there was an inverse association between log C2 and sputum neutrophil count ($r= -0.215$, p 0.047).

The results of our more extensive validation of the Leicester cough algorithm for ambulatory 24-h recordings are consistent with our previous report of 6-h daytime cough numbers. The large difference in cough frequency in health and disease, the ability of the system to detect expected sex differences in cough frequency, and the correlation seen with other measures of cough severity suggest that the automated system produces valid and potentially clinically useful data. One important caveat is that automated cough analysis inevitably results in false-positive detection of cough like sounds. This is likely to explain the tendency for cough counts to be higher when assessed using the automated system and the less close agreement between automated and manual counts in the healthy volunteers (where cough frequency is low) compared to patients.

Patients with respiratory disease had a marked increase in 24-h cough frequency but the diurnal pattern of coughing was similar. We did not show a significant increase in cough frequency in healthy smokers although larger studies which control for the healthy smoker affect might. There was a significant increase in cough frequency in males taking ACEi, a finding that is consistent with evidence that ACEi cause cough and a heightened cough reflex [9]. Our primary motive for studying patients with respiratory disease was to further validate our cough detection system. The numbers studied were small and larger studies are required to address between condition differences. However, one notable finding was the exceptionally high cough frequency in patients with unexplained chronic cough.

We found moderate correlations between 24-h cough frequency and other objective and subjective measures of cough severity suggesting that these measures provide different, potentially complimentary information on cough severity. Cough frequency was clearly different in healthy controls and patients with respiratory disease whereas there was considerable overlap between the groups in capsaicin cough reflex sensitivity. This implies that cough in disease is a function of an increased cough reflex and other, potentially disease-specific factors. The correlation between sputum neutrophil count and cough frequency

TABLE 1 Demographics of subjects

	Healthy	Smokers	ACEi	UCC	CVA/EB	COPD	Bronchitis	Asthma	ILD
Female n (%)	44 (27)	6 (3)	4 (0)	34 (27)	8 (7)	9 (5)	5 (2)	9 (5)	3 (1)
Age yrs	55 (20–80)	40 (23–55)	64 (37–80)	60 (46–80)	64 (43–68)	68 (59–80)	65 (59–69)	52 (22–77)	54 (35–67)
BMI kg·m^{-2}	26$\pm$6	23$\pm$4	28$\pm$3	27$\pm$4	34$\pm$8	23$\pm$4	28$\pm$4	31$\pm$5	30$\pm$3
FEV$_1$ % pred	99$\pm$14	93$\pm$11	102$\pm$19	91$\pm$10	96$\pm$16	64$\pm$16	63$\pm$33	85$\pm$12	87$\pm$10
FEV$_1$/FVC	80$\pm$5	81$\pm$5	80$\pm$5	76$\pm$6	80$\pm$6	56$\pm$13	68$\pm$21	74$\pm$6	87$\pm$10
Sputum eosinophils %	0.41$\pm$0.6	0.4$\pm$0.1	1.3$\pm$1.2	0.51$\pm$0.5	0.53$\pm$0.7	0.73$\pm$0.5	0.41$\pm$0.7	0.22$\pm$0.6	0.46$\pm$0.65
Sputum neutrophils %	49$\pm$29	76$\pm$16	75$\pm$22	72$\pm$14.8	60$\pm$25.7	59$\pm$27.6	84.4$\pm$13.8	63.3$\pm$18.9	65.8$\pm$10.6
C2 μmol·L^{-1}	8.7 (0.8)	6.2 (0.6)	2.6 (1.1)	1.3 (0.5)	1.45 (0.8)	0.6 (0.5)	1.3 (0.7)	1.49 (1.1)	0.05 (2.3)
C5 μmol·L^{-1}	85.66 (1.2)	26.3 (0.6)	61.7 (2.1)	35.8 (0.4)	61 (0.9)	24 (0.8)	64 (0.5)	15.7 (0.8)	19 (0.5)
LCQ[#]				11.4$\pm$3.9	8.2$\pm$3.7	12.9$\pm$3.6	14.1$\pm$5.8	11.5$\pm$5.3	14.2$\pm$7.1
VAS[¶] mm				52$\pm$4	45$\pm$12	40$\pm$6	30$\pm$9	23$\pm$5	53$\pm$19
Total coughs per 24 h	18.6 (0.5)	33 (0.6)	128 (0.2)	477 (0.3)	321 (0.3)	213 (0.3)	106 (0.7)	107 (0.3)	274 (0.8)

Data are presented as median (interquartile range), mean$\pm$SD or geometric mean (log$_{SD}$), unless otherwise stated. ACEi: angiotensin converting enzyme inhibitors; UCC: unexplained chronic cough; CVA: cough variant asthma; EB: eosinophilic bronchitis; COPD; chronic obstructive pulmonary disease; ILD: interstitial lung disease; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; C2: concentration of capsaicin required to elicit two coughs; C5: concentration of capsaicin required to elicit five coughs; LCQ: Leicester Cough Questionnaire; VAS: Visual Analogue Score. [#]: the LCQ is a 19-item validated quality of life questionnaire for patients with chronic cough. It assesses three domains (physical, psychological and social); the total score range is 3 to 21 and a higher score indicates a better quality of life. [¶]: the VAS is a 100-mm score set at 0 and 100 by ''no cough'' and ''worst cough ever'', respectively.

suggests that neutrophilic airway inflammation may be one such factor although this relationship may be a consequence of coughing rather than causal.

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Pleuroparenchymal fibroelastosis as a manifestation of chronic lung rejection?

To the Editor:

Idiopathic pleuroparenchymal fibroelastosis is a peculiar pulmonary fibrosis proposed by FRANKEL *et al*. [1] in 2003 and is almost the same concept as idiopathic pulmonary upper lobe fibrosis proposed by AMITANI *et al*. [2]. There are no known causes for fibrosis in idiopathic pleuroparenchymal fibroelastosis. Sometimes, pleuroparenchymal fibroelastosis (PPFE) has underlying diseases or conditions, such as collagen vascular diseases, anti-cancer chemotherapy, irradiation, asbestos exposure and bone-marrow transplantation [3]. Herein, we report the case of a female who received living-donor lung transplantation and died of pulmonary fibrosis, which was pathologically compatible with PPFE in addition to constrictive bronchiolitis, which is a manifestation of chronic lung allograft dysfunction (CLAD) [4].

A 30-yr-old female suffering from idiopathic pulmonary arterial hypertension underwent living-donor lung transplantation surgery and received a right lower lobe from her younger sister and a left lower lobe from her mother in December 2003. 20 months after the lung transplantation she had dyspnoea and a chest radiograph disclosed bilateral ground-glass shadows. 1 month later, right open lung biopsy was performed and a diagnosis of interstitial pneumonia was obtained. Pulse therapy with methylprednisolone slightly improved her condition and prednisolone was administered after the pulse therapy. However, bilateral interstitial opacities gradually deteriorated (fig. 1) with increased dyspnoea. 49 months after the lung transplantation, her daily life had worsened to almost whole-day bed rest. 18 days prior to her death she noticed fever and general fatigue and was admitted to our hospital (Dept of Respiratory Medicine, Fukuoka University Hospital, Fukuoka, Japan). Pulse therapy using methylprednisolone and antimicrobial and antifungal drugs were administered, without effect. She died 52 months after the lung transplantation. Histological specimens (figs 1a and b) were obtained at autopsy and chest computed tomography (fig. 1c) was obtained 51 months after lung transplantation (1 month before her death). The autopsy revealed a fibrously thickened visceral pleura and marked deposition of elastin just beneath the thickened pleura in both lungs. Alveoli filled with collagen (intra-alveolar fibrosis) were found around the border between the subpleural elastosis and the less involved lung parenchyma. There were foci of constrictive bronchiolitis surrounded by intra-alveolar fibrosis in the lung parenchyma, away from the pleural/subpleural fibrosis and elastosis. The pleural fibrosis, subpleural elastosis and intra-alveolar fibrosis observed in the present case were identical to the pathological features of PPFE described by FRANKEL *et al*. [1] and were considered as pulmonary fibrosis secondary to lung transplantation.

In 2003, KONEN *et al*. [5] reported fibrosis of the upper lobes in seven lung transplant recipients. In 2005, PAKHALE *et al*. [6] also