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Silent aspiration in patients with exacerbation of COPD

To the Editor:

Patients with chronic obstructive pulmonary disease (COPD) are susceptible to aspiration, probably due to discoordination between breathing and swallowing, cricopharyngeal muscle dysfunction, and changes in lung volume [1, 2]. Terada *et al.* [3] found a significantly higher prevalence of an abnormal swallowing reflex in patients with COPD than in healthy controls. Shaker *et al.* [4] found that patients with acute exacerbation of COPD (AECOPD) have a higher risk of aspiration. In this cross-sectional study, using the technetium-99m–sulfur colloid (^{99m}Tc-SC) salivary scintigraphy method that is believed to be more sensitive than techniques using in previous studies, the prevalence and risk factors of silent aspiration in hospitalised AECOPD patients was studied.

In this study, hospitalised AECOPD patients were recruited from the Guangzhou Institute of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, between December 2011 and August 2012. The study protocol was approved by the Scientific Research Ethics Review Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number 2012/44). The clinical trial registration number is ChiCTR-CCH-12002918 (www.chictr.org.cn). Written informed consent was received from all patients participating in the study.

The inclusion criteria for patients with COPD were: age ⩾50 years; smoking history of ⩾30 years; medical history, physical examination, chest imaging and previous pulmonary function tests supportive of a diagnosis of COPD [5]; ratio of post-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity <70%; and admission into hospital due to AECOPD [6]. The exclusion criteria were as follows:

respiratory diseases other than COPD; pre-existing neurological disorders, such as stroke and Parkinson's disease; history of oral, throat or oesophageal surgery; radiotherapy; obvious symptoms of aspiration or tracheo-oesophageal fistula; endotracheal intubation in the preceding 3 months; and dysphagia.

During the study period, 62 patients with COPD were admitted to the hospital because of acute exacerbation. 42 of these patients met the inclusion criteria and participated in the study as the AECOPD group. The normal control group was recruited from the Healthy Check-up department of First Affiliated Hospital of Guangzhou Medical University. Among the 35 age-matched subjects screened, 13 subjects met the inclusion criteria and agreed to participate in the study. Inclusion criteria for the healthy control group were: no history of major disorders; no a history of smoking; and no condition that could affect assessment of aspiration (including endotracheal intubation, central nervous system disorders, gastro-oesophageal disease, respiratory disease or symptoms such as dysphagia).

Patient's assessment included physical examination, severity of dyspnoea using the modified Medical Research Council (mMRC) dyspnoea scale [7] and chest radiography, and body mass index (BMI) was calculated. The documentation of maintenance medication and frequency of exacerbation in the previous year was evaluated by patient report, and checking the patient's clinic visit and hospital records as well as drug prescriptions. Radionuclide imaging with ^{99m}Tc-SC was performed when the patient was stable and ready for hospital discharge. The presence of radioactivity in the main bronchi or their branches was classified as aspiration (figure 1) [8].

The main findings of the study are as follows. There were no significant differences in age and BMI between the AECOPD and the control group (age 72.0±9.13 *versus* 67.62±9.38 years; BMI 19.54±3.12 *versus* 21.07±2.27 kg·m^{-2}). However, in the AECOPD group, the smoking index was higher (42.93±14.5 *versus* 0) and the FEV1 (0.84±0.41 *versus* 2.03±0.23 L and 32.68±13.2% *versus* 86.23±4.15% predicted) was lower than in the control group (all p<0.01).

Rates of positive silent aspiration were 33.3% in the AECOPD group and 0% in the control group (14 out of 42 *versus* 0 out of 13; p=0.024).

The AECOPD group was divided into the subgroups of positive silent aspiration (aspiration group, n=14) and no aspiration (n=28). The aspiration group had significantly higher mMRC dyspnoea score (p=0.020) and prevalence of exacerbation in the past year (12 out of 14 *versus* 10 out of 28; p=0.002) than the no-aspiration group.

For analysis of risk factors for silent aspiration, dependent variables included maintenance medication treatment, smoking, BMI, mMRC dyspnoea grade and FEV1 (% predicted). Logistic regression showed that mMRC dyspnoea grade was a significant risk factor associated with silent aspiration in the AECOPD group (partial regression coefficient 0.761, p=0.030; OR 2.141, 95% CI 1.078–4.25) after adjustment for confounding factors.

The abnormal swallowing function and aspiration in stable COPD or AECOPD have been a concern for decades. In 1987, Coelho [9] reported that 10 out of 14 patients with COPD had difficulty swallowing and that three (21%) had aspiration as demonstrated with video fluoroscopy. Stein *et al.* [1] reported that 17

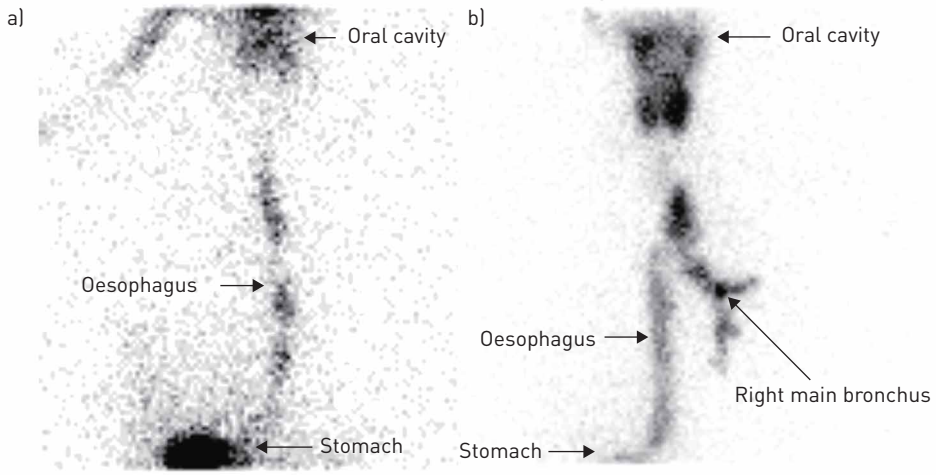

FIGURE 1 Technetium-99m–sulfur colloid scintigraphy. a) If radioactivity was present in the stomach but not in the main bronchi or their branches, the test was considered negative for aspiration; b) the presence of radioactivity in the main bronchi or their branches was classified as aspiration.

out of 25 patients with moderate-to-severe COPD developed different degrees of cricopharyngeal muscle impairment. In 2011, Cvejic *et al.* [10] conducted a study in 16 patients with stable COPD and 15 healthy individuals using video fluoroscopic swallowing study. Four patients with COPD and one healthy control had obvious aspiration. Our study with a radionuclide imaging method showed that the prevalence of silent aspiration was 33.3% (14 out of 42) in hospitalised AECOPD patients and silent aspiration was associated with the frequency of acute exacerbation in the previous year. We supposed the radionuclide imaging method we used is more sensitive and reliable for detecting silent aspiration in COPD. A comparison study of methodology for detection of aspiration is needed.

The mechanisms of higher prevalence of aspiration in COPD patients are not clear. The risk factors reported include dyspnoea, dysphagia, emphysema, weakness or incoordination of throat muscles, decreased throat sensitivity, and an impaired cough reflex [11]. It was reported that changes in lung volume or pleural pressure could affect swallowing [12, 13]. Increased lung volume reduces the number of swallows after injection of water into the throat. Increased negative pleural pressure leads to chronic aspiration by widening the difference between oropharyngeal and pleural pressure during swallowing. COPD is characterised by limitation of airflow, increased total lung capacity and dynamic hyperinflation during exercise [14]. Patients with worsened dyspnoea show more negative intrathoracic pressure. However, aspiration can worsen dyspnoea [15], further increasing the risk of aspiration by accelerating the respiratory rate and enhancing negative pleural pressure [4, 13], leading to vicious cycle of increased risk of aspiration. In our study, it was found that dyspnoea was a risk factor for aspiration. Further studies are required to fully understand the potential mechanisms for increased prevalence of aspiration.

Several limitations of the present study should be considered. Firstly, the retrospective assessment of the frequency of AECOPD may be inaccurate as the patient might forget the exact number of exacerbations. We have tried our best to improve the accuracy by checking the patients' clinic visit and hospital records. Secondly, several important factors, such as medication and smoking, might have impact on aspiration and exacerbation. These require proper controlled study to elucidate their impact. Thirdly, it is necessary to conduct a prospective follow-up study to compare the long-term outcomes of COPD patients with or without silent aspiration.

In conclusion, using scintigraphy as a diagnostic method, it was shown that the silent aspiration rate in admitted AECOPD patients was high (up to 33.3%). Positive silent aspiration was associated with more frequent exacerbation of COPD in the previous year. The clinical significance of silent aspiration deserves prospective, controlled follow-up study in the future.

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Radionuclide imaging of silent aspiration
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Susceptibility genes for lung diseases in the major histocompatibility complex revealed by lung expression quantitative trait loci analysis

To the Editor:

The major histocompatibility complex (MHC) has been linked with hundreds of diseases [1]. The MHC is one of the most complex regions of the human genome, because of the high gene density, extended linkage disequilibrium (LD) and sequence diversity [2]. Recent genome-wide association studies (GWAS) have identified polymorphisms located in the MHC that are associated with lung diseases and related traits: asthma, cystic fibrosis, idiopathic interstitial pneumonia, lung cancer and lung function. However, due to the limitations of GWAS and tissue-specific characteristics of gene expression [3], the causal genes and genetic mechanisms mediating the heritable risk within this locus remain to be found.

The present study has two goals: 1) to identify lung expression quantitative trait loci (eQTL) within the MHC region; and 2) to identify new susceptibility genes for lung diseases/traits by overlaying lung eQTL results and MHC single nucleotide polymorphisms (SNPs) previously associated with lung function and respiratory diseases. Susceptibility alleles for respiratory diseases that function as strong lung eQTL should facilitate the biological interpretation of GWAS results and the identification of causal genes in loci with high gene density and high LD such as the MHC.

Study subjects and lung specimens have been described previously [4]. Subjects were from three academic sites: Laval University (Quebec, Canada), University of British-Columbia (Vancouver, Canada) and Groningen University (Groningen, the Netherlands), henceforth referred to as Laval, UBC and Groningen, respectively. Genome-wide gene expression and genotyping profiles were obtained using a custom Affymetrix array (GPL10379; Affymetrix, Santa Clara, CA, USA) and the Illumina Human1M-Duo BeadChip array (Illumina, Inc., San Diego, CA, USA), respectively. Only subjects that passed genotyping and gene expression quality controls [5] were included in this study. Subjects with missing values for smoking status were also excluded, leaving 409, 287 and 342 subjects from Laval, UBC and Groningen, respectively.

The borders of the extended MHC (xMHC) were defined [1] and delimited by two genes on chromosome 6: *HIST1H2AA* and *KIFC1*. The expressions of all probe sets located within this region were analysed, which included 271 probe sets covering 212 transcripts. 6872 genotyped SNPs were available in the three datasets. Lung eQTL in the xMHC region were identified with expression data adjusted for age, sex and smoking status [5]. Association tests between adjusted expression traits and SNPs were performed using quantitative