

Detection of salivary aspiration using radionuclide salivagram SPECT/CT in patients with COPD exacerbation: a preliminary study

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Background: The aim of this prospective study was to assess the utility of radionuclide salivagram for detecting salivary aspiration in AECOPD patients and to evaluate the adding value of SPECT/CT to planar imaging.

Methods: 52 consecutive AECOPD patients underwent radionuclide salivagram SPECT/CT and water swallow test between April 2012 and March 2014. All images were interpreted independently by two experienced nuclear medicine physicians. Final diagnosis was made by consensus of two readers. The radionuclide salivagram and water swallow test results were compared using kappa values. The relationship between radionuclide salivagram results and exacerbation frequency was evaluated with the Person χ^2 test.

Results: Salivary aspiration was diagnosed by radionuclide salivagram in 17 of 52 patients. Aspiration into the right main bronchus and branch was seen in 8 patients, bilateral main bronchi in 6 patients, and left lung field in 3 patients. SPECT/CT provided more accurate information on the extent and location of salivary aspiration, in 11 cases, SPECT/CT demonstrated aspiration of pulmonary segment bronchus and the following areas. Moreover, SPECT/CT revealed salivary aspiration corresponding to aspiration pneumonia in 8 cases. There was general agreement between the radionuclide salivagram and water swallow test results (Kappa =0.712; 95% CI, 0.504–0.920; P<0.001). The incidence of frequent exacerbations was greater among subjects with positive salivagram than among those with negative salivagram results (RR =3.43; 95% CI, 1.90–6.19; P<0.001).

Conclusions: Radionuclide salivagram is an objective method for detecting salivary aspiration in AECOPD patients. Moreover, SPECT/CT can identify more precise location of salivary aspiration and suggest a possible role for saliva in the pathophysiology of aspiration pneumonia.

Keywords: Chronic obstructive pulmonary disease (COPD); exacerbation; aspiration; SPECT/CT; radionuclide imaging

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major public health problem. The acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with the worsening of symptoms and quality of life, as well as an increased morbidity and mortality (1-3). COPD exacerbations can be precipitated by several factors, the most common of which is respiratory tract infection. However, the cause of approximately one-third of severe COPD exacerbations cannot be identified. Several studies have shown that COPD exacerbations may be associated with aspiration (4-8).

Pulmonary aspiration can occur as a result of swallowing dysfunction, gastro-oesophageal reflux, or an inability to adequately protect the airway from oral secretions. Chronic aspiration of saliva is the least-commonly recognized form of aspiration and is usually not diagnosed prior to the development of significant lung injury. In addition, there is currently no standard test for the detection and evaluation of salivary aspiration. The role of salivary aspiration in COPD exacerbation has not been demonstrated convincingly. If salivary aspiration is confirmed to be an important precipitant or aggravating factor of COPD exacerbations, strategies to prevent aspiration have the potential to improve quality of life and survival and reduce health care costs.

Radionuclide salivagram is a useful method for detecting salivary aspiration during small bolus swallows. However, it is mostly used in pediatric patients (9-12), and no previous study has assessed its utility in AECOPD patients. Furthermore, in all studies of radionuclide salivagram, only traditional planar images were obtained, and the poor spatial and temporal resolution of planar images and the lack of anatomic landmarks are limiting factors. Single photon emission computed tomography/computed tomography (SPECT/CT) allows the coregistration of functional and anatomic imaging and has been used for a wide array of oncologic and non-oncologic indications (13-15). However, no study to date has examined the clinical value of the combination of planar images and SPECT/CT fusion images for the detection of salivary aspiration.

Therefore, the purpose of this study was to assess the utility of radionuclide salivagram for detecting salivary aspiration in AECOPD patients. This study also evaluated the added value of SPECT/CT in combination with radionuclide salivagram for detecting salivary aspiration in AECOPD patients.

Methods

Patients

Consecutive AECOPD patients at Guangzhou Institute of Respiratory Disease were enrolled in this study between April 2012 and March 2014. The inclusion criteria were the following: (I) ≥ 50 years of age; (II) smoking history of ≥ 30 packs of cigarettes per year; (III) medical history and physical examination, chest radiography, and pulmonary function test (PFT) results consistent with the diagnosis of COPD; (IV) ratio of post-bronchodilator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) of 70% or less; and (V) case fulfills COPD exacerbation criteria (worsened dyspnoea, increased cough and/or expectoration beyond the daily variation, and requirement for additional drug therapy). The exclusion criteria were the following: (I) previous history of swallowing problems; (II) known neurological disease; (III) known gastro-oesophageal reflux disease; and (IV) incomplete information.

Our final study population included 52 AECOPD patients (5 women and 47 men; age range, 53–88 years, mean age: 73 ± 9 years). Patient characteristics are shown in *Table 1*. History assessment, physical examination, calculation of body mass index (BMI), exacerbation frequency in the past year, chest radiography and the modified Medical Research Council (mMRC) dyspnoea scale were evaluated after admission. Water swallow test (a widely used test for aspiration) and radionuclide salivagram were performed on the day immediately before hospital discharge for all subjects. This study was approved by the Scientific Research Ethics Review Committee of the First Affiliated Hospital of Guangzhou Medical University, and all subjects signed a written informed consent form.

Water swallow test

Patients were asked to drink 30 mL of water without interruption. Any coughing or throat clearing was indicative of an abnormal water swallow test. The water swallow test results were classified as follows: grade 1: no interruption, no choking or coughing; grade 2: two or more interruptions, no choking or coughing; grade 3: no interruption, with coughing; grade 4: more than two interruptions, with choking; grade 5: frequent cough, cannot swallow entirely. Patients with grade 3 to 5 results were considered positive for aspiration.

Table 1 Patient characteristics

Characteristic	Data
No. of subjects (%)	52 (100.0)
Female (%)	
Male	47 (90.4)
Female	5 (9.6)
Age (years)	
Mean \pm SD	72.8 \pm 8.9
Range	53–88
BMI (kg/m ²)	
Mean \pm SD	19.6 \pm 3.0
Range	14.7–31.2
FEV ₁ (L)	
Mean \pm SD	0.8 \pm 0.4
Range	0.3–2.2
%FEV ₁	
Mean \pm SD	35.8 \pm 16.6
Range	13.5–90.6
The frequency of exacerbations during the past year (%)	
\geq 2	24 (46.2)
<2	28 (53.8)
mMRC dyspnoea (score) (%)	
Grade 0 or grade 1	10 (19.2)
Grade 2	11 (21.2)
Grade 3	23 (44.2)
Grade 4	8 (15.4)

Data are presented as No. (%), BMI, body mass index; mMRC, modified medical research council.

Radionuclide salivagram

Preparation of radioactive tracer

The radiopharmaceutical was Tc-99m sulphur colloid (SC). It was prepared using kits provided by Guangzhou Atom High-tech Isotope Pharmaceutical Co., Ltd. (Guangzhou, China) that contained 3 separate nonradioactive components: (I) 1.5 mL solution of 0.148 N HCl in a reaction vial; (II) 1 mL solution of 2.0 mg sodium thiosulfate, 18.1 mg gelatin (porcine), and 2.3 mg sodium edetate; and (III) 1 mL solution of 0.8 M phosphate buffer. Tc-99m SC

was prepared by adding 1–3 mL of Tc-99m pertechnetate to the reaction vial at a dosage of 3,700–7,400 MBq (10–20 mCi) and then immediately adding component B. Next, the vial was placed into a boiling water bath for 3 min. Finally, the vial was cooled, and component C was added, and the solution was mixed thoroughly.

Radionuclide salivagram dynamic acquisition

Salivagram was performed using a modification of the method reported previously (9,16). The radiopharmaceutical was Tc-99m SC at a dosage of 74.0 MBq (2 mCi) in 20 mL normal saline in a syringe. The syringe was attached to an infusion prolonged tube (150 cm in length and 0.1 cm in diameter), and the distal end of the tube was placed inside the mouth of the patient. Tc-99m SC was continuously infused into the oral cavity using a micro-injection pump (WZ-50C6T, Zhejiang University Medical Instrument Co., Ltd. Zhejiang, China) over 30 min.

No patient preparation was required before the examination. During this period, the patients were asked to maintain normal swallowing activity. Imaging was performed using a Siemens Symbia T16 SPECT/CT system (Siemens Healthcare, Munich, Germany) with a 128 \times 128 matrix and a low energy high resolution (LEHR) collimator and Zoom of 1.45. Patients were allowed to swallow naturally in the supine position, and posterior planar images from the mouth to the stomach were obtained. The dynamic acquisition occurred over 30 min at a rate of one frame per 30 s. If no radioactivity was detected in the bronchi or lungs throughout the dynamic acquisition, static images in the anterior and posterior projections were acquired with 5-min delay at 6 h after the radiopharmaceutical instillation with a 256 \times 256 matrix, and Zoom of 1.45.

SPECT/CT acquisition

If the dynamic acquisition was positive for aspiration, the patients were given 100 mL of water to drink, and then SPECT/CT fusion images were obtained. SPECT scanning was performed in a 64 \times 64 matrix over 360° (with a 6° step and 20 s per frame). CT was then performed in the same position (130 kV and 80–120 mA) with a slice thickness of 3 mm.

Image interpretation

All images were interpreted independently by two experienced nuclear medicine physicians without knowledge of the subjects' histories. The final diagnosis was obtained by consensus of the two readers. The images were analyzed

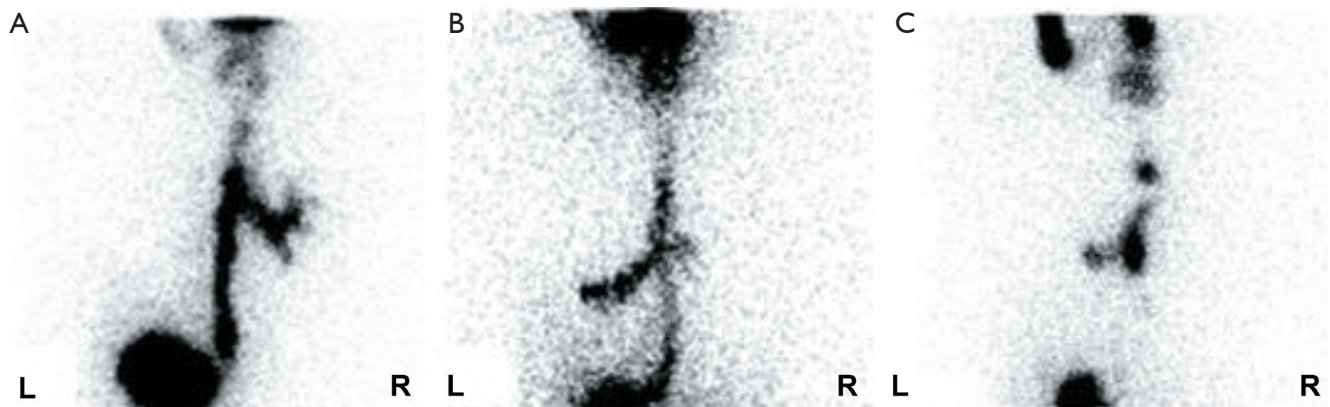


Figure 1 Representative positive radionuclide salivagram in AECOPD patients. (A) Salivary aspiration was seen in right main bronchus and branch; (B) salivary aspiration was seen in bilateral main bronchi; (C) salivary aspiration was seen in left main bronchus.

by visual interpretation as follows:

Positive aspiration: Radioactivity present in the bronchus and/or lung fields (*Figure 1*). **Negative aspiration:** No evidence of radioactivity in the bronchi or lungs. Radiotracer activity only observed from the mouth through the esophagus and into the stomach. The severity of aspiration was scored as grade 1 if the activity was only present in the location of the main bronchi and grade 2 if the activity was also present in the more peripheral bronchi ramifications (17).

Statistical analysis

The results are expressed as the means \pm SD or medians. The radionuclide salivagram and water swallow test results were compared using kappa values, with excellent agreement represented by kappa values greater than 0.75. The relationship between radionuclide salivagram results and exacerbation frequency was evaluated with the Person χ^2 test, and 95% confidence intervals (CI) were calculated. P values less than 0.05 were considered to indicate a statistically significant difference. Statistical calculations were performed using the SPSS18.0 software.

Results

Frequency and time of salivary aspiration

All subjects completed the radionuclide salivagram, and they did not complain of any discomfort. Salivary aspiration was diagnosed by radionuclide salivagram in 17 of the 52 AECOPD patients (33%) and was excluded in the other 35 patients (67%). Among the positive salivagram cases,

aspiration into the following areas was observed: right main bronchus and branch in 8 patients (47%), bilateral main bronchi in 6 patients (35%), and left lung field in 3 patients (18%). In regards to aspiration severity, 3 cases were classified as grade 1 and 14 as grade 2. Regarding the timing of visualization of salivary aspiration after oral administration of the radiotracer, the earliest was at 3 min, and the latest was at 25 min (median 20 min).

SPECT/CT findings

A total of 13 AECOPD patients with positive aspiration underwent SPECT/CT fusion images. SPECT/CT provided more accurate information on the extent and location of salivary aspiration. Radiotracer was present at the bronchus level in 2 out of 13 patients, and this SPECT/CT finding was consistent with the planar imaging findings. Radiotracer was present at the level of the segmental bronchus and beyond in 11 out of 13 patients (*Figure 2*). However, in those patients, planar imaging did not identify the actual level of penetration of the radiotracer. Moreover, SPECT/CT revealed salivary aspiration caused aspiration pneumonia in 8 cases (*Figure 3*).

Comparison of radionuclide salivagram and water swallow test results

Eleven of 52 patients had a positive water swallow test. Six patients with positive salivary aspiration findings on salivagram had negative water swallow test results; whereas, all patients with abnormal water swallow test results were positive for salivary aspiration on salivagram (*Table 2*).

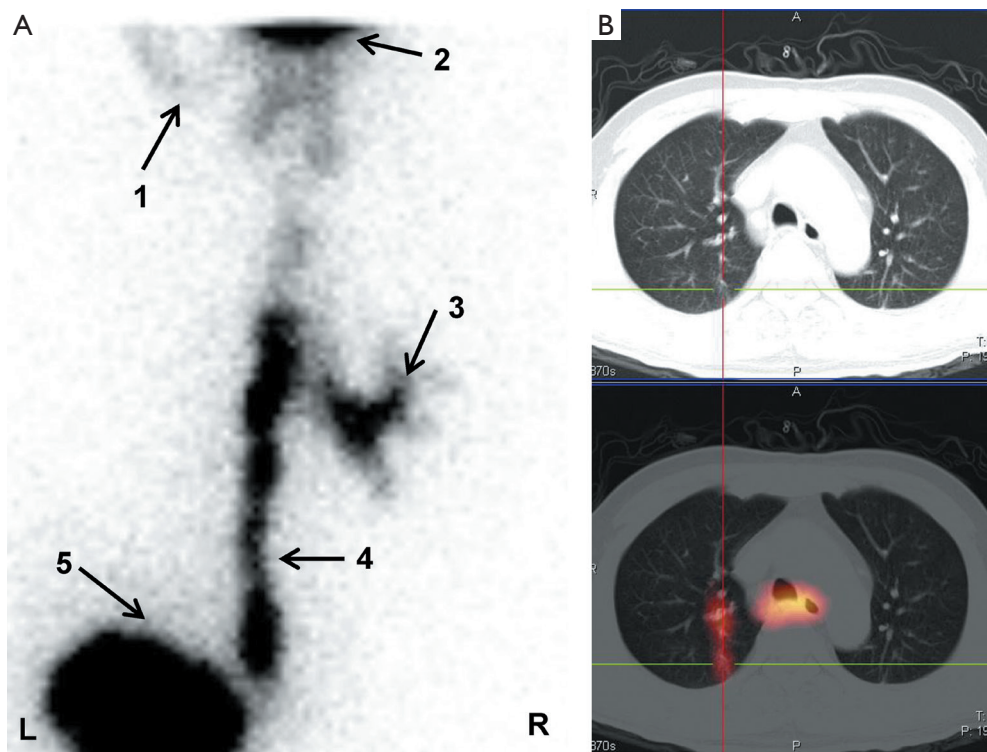


Figure 2 A 71-year-old male patient with AECOPD. (A) Radionuclide salivagram showed salivary aspiration into right main bronchus and branch (arrow 3); (B) SPECT/CT imaging showed precise anatomic location and extent of salivary aspiration in right upper lobe apical and posterior segment (cross mark). Arrow 1, infusion prolonged tube; arrow 2, oral cavity; arrow 4, esophagus; arrow 5, stomach.

There was general agreement between the radionuclide salivagram and water swallow test results (Kappa =0.712; 95% CI 0.504–0.920; $P<0.001$).

Correlation between radionuclide salivagram and exacerbation frequency

Frequent exacerbations were defined as an annual occurrence of ≥ 2 (18). The incidence of frequent exacerbations was greater among subjects with positive salivagram than among those with negative salivagram results (RR =3.43; 95% CI, 1.90-6.19; $P<0.001$) (Table 3).

Discussion

Radionuclide salivagram is an objective method for detecting salivary aspiration. The unique advantages of salivagram include the following: (I) safety and ease of performance; (II) ease of acceptance and cooperation of patients; (III) consistency with normal physiological swallowing conditions; (IV) ability to reveal more distal

penetration (19); and (V) long-term monitoring. Our study of radionuclide salivagram showed that salivary aspiration was frequent (33%) in AECOPD patients, which suggests that salivary aspiration plays an important role in COPD exacerbation.

The localization of salivary aspiration is related to the construction of each bronchial tree and the posture of the patient during aspiration. In our study, the most common location of salivary aspiration was the right main bronchus and branch, which is due to the vertical position of the right main bronchus and its larger diameter compared to the left main bronchus. As salivary aspiration events often occur intermittently, dynamic imaging can detect salivary aspiration during swallowing for a long duration. Therefore, this approach is useful to improve the detection accuracy of salivary aspiration. All salivary aspiration was observed in the initial dynamic acquisition phase of the study, which is consistent with the previously reported data (12). However, the occurrence time of aspiration varied among the included patients; thus, further studies are needed to determine whether aspiration time point is associated with the severity

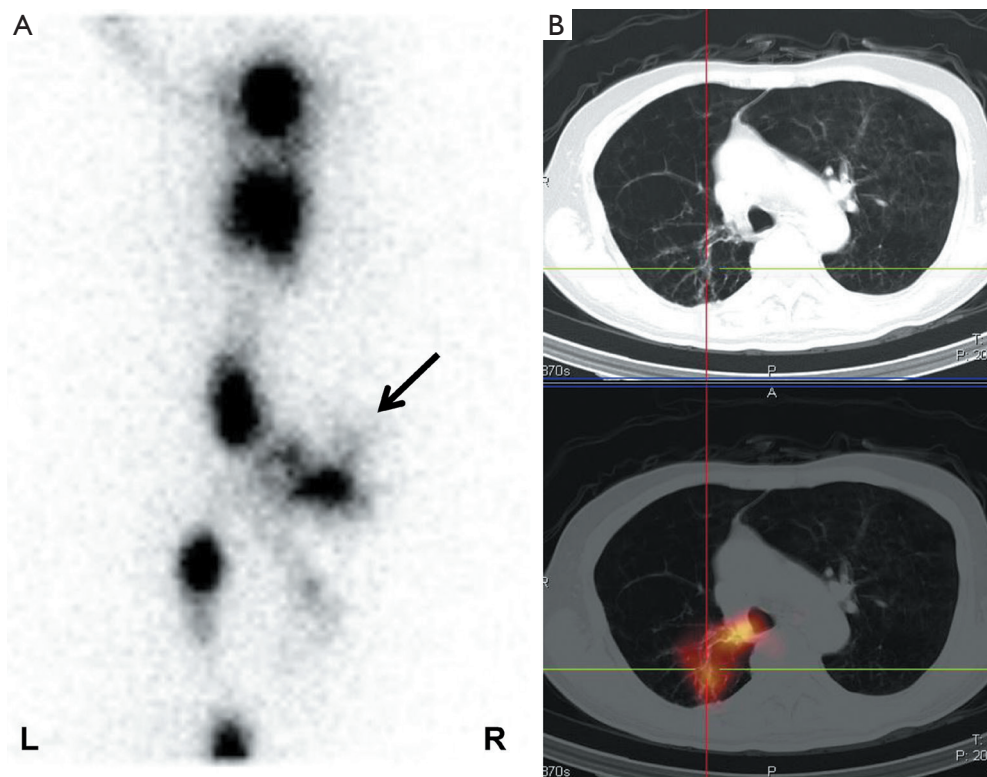


Figure 3 A 68-year-old male patient with AECOPD. (A) Radionuclide salivagram showed positive salivary aspiration in right main bronchus and branch (arrow); (B) SPECT/CT imaging revealed salivary aspiration resulted into pneumonitis in right upper lobe posterior segment (cross mark).

Table 2 Correlation between water swallow test and radionuclide salivagram in AECOPD patients

Water swallow test	Salivagram		Total
	Positive	Negative	
Positive	11	0	11
Negative	6	35	41
Total	17	35	52

Data are presented as number. Agreement between radionuclide salivagram, and water swallow test was general (Kappa =0.712; 95% CI, 0.504–0.920; $P < 0.001$).

of AECOPD.

Pulmonary aspiration can be assessed by a number of methods, including clinical assessment (e.g., water swallow test), videofluoroscopic swallowing study (VFSS), and fiberoptic endoscopic evaluation of swallowing (FEES). The water swallow test is a widely used test for aspiration that is perceived to be simple and easy to perform and can be

Table 3 Associations between exacerbations and radionuclide salivagram in AECOPD patients

Salivagram	COPD exacerbation		Total
	Occurred	Not occurred	
Positive	15	2	17
Negative	9	26	35
Total	24	28	52

Data are presented as number. Frequent exacerbations were defined as an annual occurrence of ≥ 2 . The incidence of frequent exacerbations was greater in subjects with a positive salivagram than in those with a negative response (RR =3.43; 95% CI, 1.90–6.19; $P < 0.001$). RR, relative risk.

repeated frequently; however, it fails to identify all patients with salivary aspiration. VFSS can be used to directly evaluate the oropharyngeal and esophageal phases of swallowing. However, it has significant false-negative results in predicting those who will progress to have aspiration pneumonia (20),

and it uses a greater radiation dose (1.23 mSv), which limits the ability to perform frequent follow-up examinations (21). FEES can be performed at the bedside and does not expose the patient to radiation; however, it is invasive and difficult to perform (18). Our study compared radionuclide salivagram and water swallow test results. Six patients with positive salivary aspiration findings on salivagram were negative on the water swallow test. Thus, 14.6% of the patients (6/41) had false negative results on the water swallow test. Therefore, a normal water swallow test result did not rule out salivary aspiration in these AECOPD patients.

In the present study, we demonstrated the clinical application of SPECT/CT for the detection of salivary aspiration in patients experiencing a COPD exacerbation. SPECT/CT provides anatomic and functional information, which has revolutionized the field of diagnostic medical imaging. The values of SPECT/CT include the following: (I) The poor spatial resolution of planar images prevents them from accurately identifying the actual level of penetration of the radiotracer in the segmental bronchus and beyond. In contrast, SPECT/CT shows the precise anatomic location of salivary aspiration. Furthermore, accurate positioning helps to identify tracheal aspiration that may otherwise be missed on planar salivagram dynamic images because of overlapping of the trachea with the esophagus. In our experience, SPECT/CT images did not identify more cases of salivary aspiration than salivagram with planar imaging; however, they did allow for more precise identification of the location of salivary aspiration. (II) Physicians require sensitive and specific imaging techniques to reflect the relationship between salivary aspiration and aspiration pneumonia. SPECT/CT fusion imaging accurately reveals the degree of respiratory tract infections caused by salivary aspiration. Salivary aspiration location is consistent with the areas of the respiratory tract that are infected. In this study, SPECT/CT provided strong evidence establishing salivary aspiration as a direct cause of respiratory tract infection.

The swallowing reflex is an important defense against airway infection resulting from the aspiration of misdirected oropharyngeal or gastric contents into the larynx and lower airway. Therefore, impairment of this reflex is directly associated with an increased risk of silent aspiration and pneumonia (22,23). In 2010, Terada *et al.* (8) found that an abnormal swallowing reflex is associated with an increased frequency of COPD exacerbations. Our results showed that salivary aspiration is associated with an increased frequency

of COPD exacerbations within the previous year. This is important for understanding the relationship between aspiration and COPD exacerbations.

In this study of AECOPD patients, we confirmed that radionuclide salivagram can identify the presence of salivary aspiration. We also showed that radionuclide salivagram with SPECT/CT is a more sensitive technique for visualizing salivary aspiration than radionuclide salivagram with planar imaging. However, this study had some limitations. First, it was performed at a single center, which may limit the generalizability of our results. Second, radionuclide salivagram was performed on the day immediately before hospital discharge for all subjects in consideration of patient safety. Therefore, our findings may only be generalizable to convalescent AECOPD patients.

Conclusions

Radionuclide salivagram is a useful method for detecting salivary aspiration in AECOPD patients. Moreover, SPECT/CT more accurately visualizes the penetration of the radiotracer than planar imaging, and the results of this study suggest a possible role of salivary aspiration in the pathophysiology of aspiration pneumonia.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the Scientific Research Ethics Review Committee of the First Affiliated Hospital of Guangzhou Medical University, and all subjects signed a written informed consent form.

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