Original article

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Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms

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Objectives **Gastro-oesophageal reflux disease (GERD) is poorly defined at best. Symptoms can be variable, ranging from none to heartburn, regurgitation and chest pain. When the reflux extends to the oropharynx [laryngopharyngeal reflux (LPR)], the symptoms can be protean and include cough and sore throat. We present the scintigraphic findings in two broad groups classified by symptoms as either GERD or LPR.**

Patients and methods **Patients with an established diagnosis of GERD or LPR by standard methods (95%) or high clinical pretest probability (5%) were scanned in the upright and supine position after swallowing ^{99m}Tc-DTPA. A delayed image was obtained at 2 h to evaluate the possibility of lung aspiration.**

Results **Studies were obtained in 285 patients (168 females, 117 males), with a mean age of 54 years. Of these, 80 had typical symptoms of GERD and 205 had LPR. The group with GERD had pharyngeal contamination in 49 and 14% showed pulmonary aspiration. The group with LPR had pharyngeal contamination in 65 and 23% had lung aspiration. Pharyngeal contamination was more common in the supine than in the upright position ($P = 0000$). Lung aspiration was correlated with upper oesophageal activity.**

Conclusion **Scintigraphic reflux studies are a good screening test for GERD and LPR as they can detect oropharyngeal reflux and lung aspiration in an unsuspected proportion of patients in both groups. The oropharynx and lung are sites that are out of reach of the current standards of investigation such as pH studies, manometry and impedance monitoring.** *Nucl Med Commun* **36:625–630**

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Keywords: cough, gastro-oesophageal reflux disease, laryngopharyngeal reflux, lung aspiration, oesophageal manometry, pH studies, scintigraphy

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Objectives

There is no clear-cut definition of gastro-oesophageal reflux disease (GERD). In 2006, the Montreal Consensus Group defined GERD as 'a condition which develops when the reflux of stomach contents causes troublesome symptoms or complications'. Symptoms include cough, sore throat, atypical chest pain and other apparent non-oesophageal symptoms. Heartburn and regurgitation are the two most common symptoms, with a small proportion of patients being asymptomatic [1,2]. GERD has a significantly different symptom profile to laryngopharyngeal reflux (LPR). LPR involves reflux of gastric contents that contaminate the larynx and pharynx, with the possibility of a reflex-mediated contribution. The major symptoms of pharyngeal inflammation may be nonspecific, presenting with chronic cough, hoarseness, throat clearing, sore throat, voice fatigue and a globus sensation.

The main problem with LPR, whether symptomatic or silent, is the risk of prolonged exposure leading to pulmonary disease secondary to lung aspiration. Symptoms may be nonspecific and suggestive of asthma, allergy, pulmonary disease, drugs and poor diagnostics [3]. There is, however, a vast array of nonspecific conditions that may be ascribed to GERD [4]. Not all chronic cough is because of LPR and the current methods of establishing LPR are flawed [5] as 50% of cases have no evidence of acid reflux on pH monitoring [6], and indirect laryngoscopy is unreliable [7].

We present data on scintigraphic studies in two distinct groups of patients with symptom profiles consistent with either proven GERD or LPR. These patients had undergone conventional manometry and 24 h pH monitoring that established the presence of GERD in both highly selected groups. The scintigraphic studies include the important assessment of tracer activity in the upper oesophagus or pharynx and lung aspiration.

Patients and methods

Population and clinical data

Patients were extracted from a research database of cases of either proven (95%) or with high clinical probability (5%) of GERD that had been approved by the Concord Hospital Ethics Committee. All patients were considered if they had symptoms typical of GERD (heartburn,

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chest pain) and abnormal oesophageal manometry or pH studies as described elsewhere [8]. Patients with predominantly upper respiratory tract symptoms who remained undiagnosed after 8 weeks of appropriate investigation were also included. The major upper respiratory tract symptoms were cough, sore throat, recurrent throat clearing, voice change, laryngospasm, aspiration, globus and regurgitation. A history of heartburn was also elicited. An experienced surgical consultant assessed the patients' histories and categorized them as having predominantly GERD or LPR symptoms.

Scintigraphy

Patients were fasted overnight and medications were ceased for the 24 h before the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, Wisconsin, USA) with markers placed on the mandible and over the stomach to ensure that the regions of interest were within the field of view of the camera. Patients swallowed 100 ml of water with 40–60 MBq of ^{99m}Tc-DTPA, followed by another 50–100 ml of water to clear the mouth and oesophagus of radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 5 min at 15 s/frame into a 64×64 matrix (Fig. 1). A second 30 min dynamic image was obtained in the supine position immediately following the upright study utilizing 30 s frames. Following acquisition of the supine study, the patients were given a further 50 ml of water with 60 MBq of ^{99m}Tc phytate (colloid), followed by 50 ml of water as a flush. Delayed images were obtained at 2 h to assess the presence of aspiration of tracer activity into the lungs. Images were analysed by time–activity curves over the pharynx, upper and lower half of the oesophagus and a background region over the right side of the chest (Fig. 2), away from the stomach and oesophagus. Delayed images were analysed by a line profile over the lungs (Figs 3 and 4). A line was scrolled down through the delayed image and the count profile was assessed for a significant spike in counts over the lung hilum and lower lobes. This was considered significant if the counts were at least twice the background activity. Different agents were used as DTPA clears rapidly from the stomach and oesophagus after reflux. The colloid will remain in the lungs if aspirated, unlike DTPA, which would be cleared from the lungs as in lung clearance studies. DTPA is also the major agent utilized in the extant literature for the initial stage of acquisition. The second dose of colloid increases the chance of detecting aspiration.

Results were recorded retrospectively in a database, showing refluxate detected over the upper oesophagus or pharynx on the erect and supine imaging, and whether aspirate was present in the lungs on delayed imaging.

Data analysis

Data were analysed using standard statistical methods as much of the analysis was of differences in the means by the two-tailed *t*-test by groups and variables. Pearson correlation coefficients (two tails) with significance levels of 0.05 were utilized when seeking correlations between the variables in each group of patients (GERD vs. LPR). Univariate and multivariate analyses were carried out to evaluate the possibility of variables predicting lung aspiration in the two groups. The Statistica V8 software (Statsoft, Tulsa, Oklahoma, USA) package was used for data analysis.

Results

Population and clinical data

There were 285 patients in total (168 females, 117 males), with a mean age of 54.4 years at scintigraphy (range 17–90 years). The group included 80 patients with symptoms suggestive of GERD (34 females, 46 males; mean age 48.9, range 17–83) and 205 patients with symptoms suggestive of LPR (134 females, 71 males; mean age 56.6, range 23–90). Symptom profiles are shown in Table 1.

Scintigraphy in the gastro-oesophageal reflux disease group

In this group of 80 patients, 22 (27.5%) refluxed tracer into the upper oesophagus on erect imaging (Fig. 1), and of these, 19 refluxed into the pharynx (23.75% of the total GERD population). On supine imaging, 41 patients (51.25%) refluxed tracer into the upper oesophagus, and of these, 39 into the pharynx (48.75% of the total GERD population). Eleven of these patients (13.75%) showed evidence of pulmonary aspiration on the delayed study (Fig. 4). These results are summarized in Table 2. No patient with an abnormal pH study was missed by the scintigraphic reflux study.

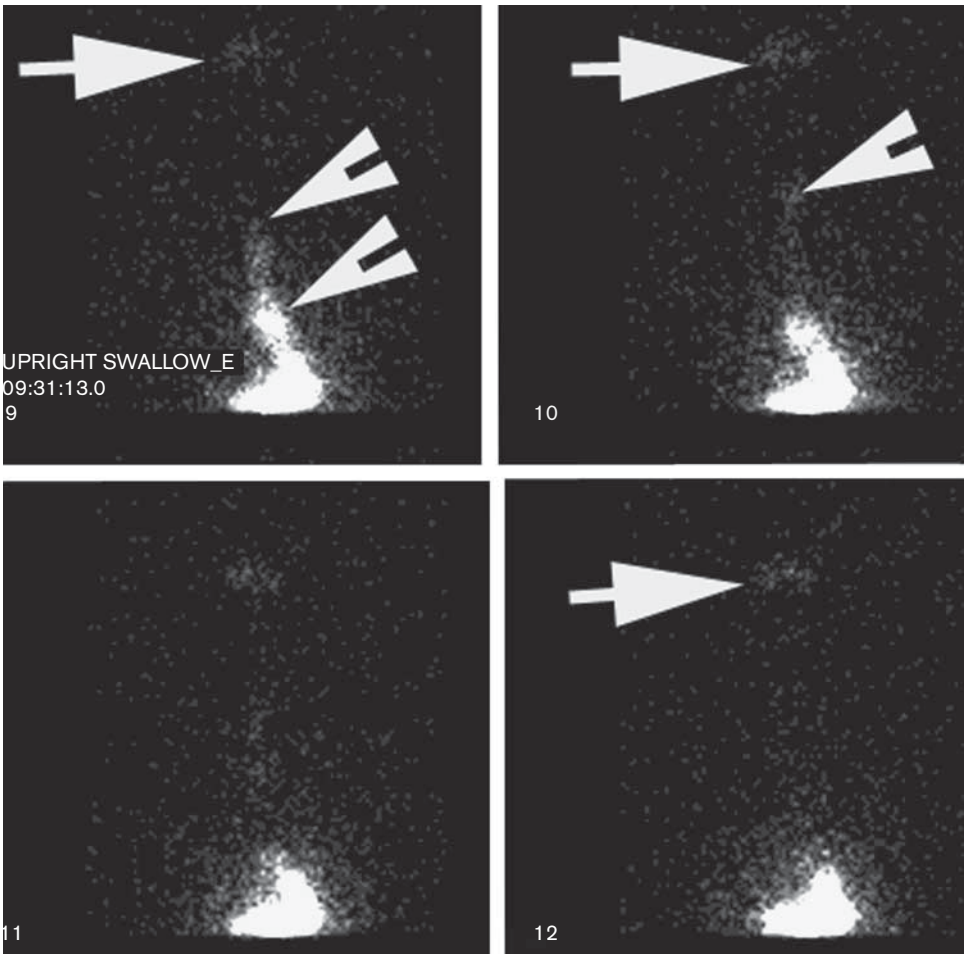
Scintigraphy in the laryngopharyngeal reflux group

In this group of 205 patients, 84 (40.98%) refluxed tracer into the upper oesophagus on the erect study (Fig. 1), and of these, 74 refluxed into the pharynx (36.1%). On supine imaging, 142 patients (69.27%) refluxed tracer into the upper oesophagus and of these, 133 refluxed into the pharynx (64.88%). Pulmonary aspiration was apparent in 48 patients (23.41%). These results are summarized in Table 3. No patient with an abnormal pH study was missed by the scintigraphic reflux study.

Statistical analysis

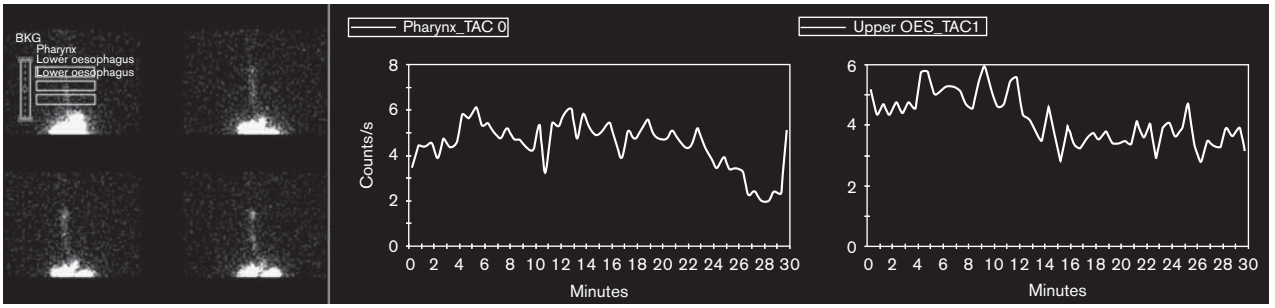
There was a significant difference between pharyngeal tracer activity in the upright and supine position for both the GERD and the LPR patients by the two-tailed *t*-test. For GERD patients, the difference was significant at a *P* value of 0.0005 ($t = 3.56$) and for the LPR patients, the difference was significant at a *P* value of 0.0000 ($t = 6.98$). A significant difference was also apparent between the supine GERD and LPR groups for pharyngeal activity, with a *P* value of 0.0084 ($t = 2.67$). Importantly, a significant difference was evident for the rates of lung

Fig. 1



Upright dynamic study. Four frames from the dynamic show full-column gastro-oesophageal reflux (arrowheads) with a progressive increase in activity in the oropharynx (arrow).

Fig. 2



Graphical analysis of activity in the upper oesophagus and oropharynx. The dynamic study in the first panel shows typical regions of interest over the pharynx, upper and lower oesophagus and background in a patient with full-column gastro-oesophageal reflux. The middle panel shows a progressive increase in activity over the pharynx with a similar initial pattern in the upper oesophagus.

aspiration in the GERD and LPR patients with a P value of 0.0026 ($t = 3.04$). There were correlations between lung aspiration, upper oesophageal upright ($P = 0.003$), upper oesophageal supine ($P = 0.029$) and pharyngeal upright ($P = 0.009$), but not pharyngeal supine ($P = 0.09$) in the GERD group. On multivariate analysis of the data

for the GERD patients, no variable was predictive of lung aspiration ($P > 0.05$). A good correlation was found between lung aspiration, upper oesophageal upright ($P = 0.000$), upper oesophageal supine ($P = 0.000$), pharyngeal upright ($P = 0.000$) and pharyngeal supine ($P = 0.006$) in the LPR group. In the LPR group, multivariate analysis found that upper oesophageal tracer activity in the supine position was predictive of lung aspiration of tracer ($P = 0.023$). Pharyngeal activity did not predict lung aspiration in either the upright or the supine position.

The power of the study for the evaluation of lung aspiration in the two groups of patients with GERD and

Table 1 Symptom profiles

GERD	Laryngopharyngeal reflux
Heartburn	Heartburn
Chest pain	Cough
	Sore throat
	Recurrent throat clearing
	Laryngospasm
	Voice change
	Aspiration
	Globus
	Regurgitation

GERD, gastro-oesophageal reflux disease.

Table 2 Presence of refluxate on reflux scintigraphy in patients with gastro-oesophageal reflux disease symptoms

GERD patients	$N = 80$ [n (%)]
Erect study	
Upper oesophagus	22 (27.50)
Pharynx	19 (23.75)
Supine study	
Upper oesophagus	41 (51.25)
Pharynx	39 (48.75)
Aspiration	11 (13.75)

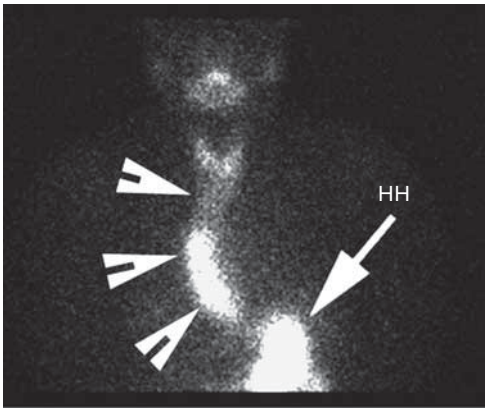
GERD, gastro-oesophageal reflux disease.

Table 3 Presence of refluxate on reflux scintigraphy in patients with LPR symptoms

LPR patients	$N = 205$ [n (%)]
Erect study	
Upper oesophagus	84 (40.98)
Pharynx	74 (36.10)
Supine study	
Upper oesophagus	142 (69.27)
Pharynx	133 (64.88)
Aspiration	48 (23.41)

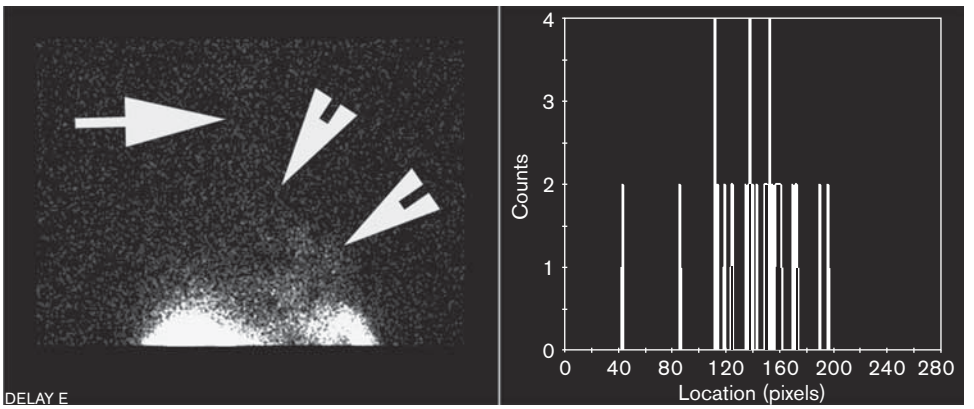
LPR, laryngopharyngeal reflux.

Fig. 3



The delayed study at 2 h shows persistent activity in the entire oesophagus (arrowheads) in a patient with a large hiatus hernia (HH, arrow). Uptake in the thyroid gland is also apparent from free pertechnetate in the colloid.

Fig. 4



Lung aspiration of tracer (arrowheads) in a patient with silent gastro-oesophageal reflux and established bronchiectasis. Note that there is no thyroid uptake in this case, indicating the absence of significant free pertechnetate that may have been taken up at the site of bronciectasis. Faint uptake is present in the oesophagus (arrow). The line profile on the right confirms persistent tracer activity in the oesophagus and at two sites in the left lower lobe (arrowheads).

LPR was 0.7, with an acceptable probability of type I or II errors.

Discussion

Traditional methods of a diagnosis for GERD have included endoscopy, pH monitoring and manometry, which provide a good assessment of the presence of acid reflux to the level of the upper oesophagus. Nonacid reflux is a major diagnostic issue [9], which has been addressed more recently by high-resolution manometry and impedance monitoring [10], which have shown promising results [11]. Impedance monitoring may also have the capacity to assess pharyngeal reflux, although reproducibility and reliability of the study may be an issue [11]. LPR poses a diagnostic problem as oropharyngeal reflux and lung aspiration are a relative blind spot for the established diagnostic techniques [12]. Scintigraphic reflux studies offer a valuable screening tool in the setting of suspected LPR (Figs 1 and 2) and may provide unexpected findings in the setting of GERD with silent LPR. Scintigraphy was applied in the setting of a highly selected group of patients with established diagnoses to evaluate its performance characteristics as a potential screening tool for pharyngeal reflux and lung aspiration.

Reflux scintigraphy is a simple and noninvasive technique. It shows direct contamination of the oropharynx and lungs by reflux disease (Figs 1 and 2). However, the technique requires strict standardization and attention to detail. Freshly prepared DTPA is a prerequisite to prevent free pertechnetate being taken up by the thyroid and salivary glands and interfering with the study. The volume of liquid in which the tracer is ingested and the framing rates are important if false-negative studies are to be avoided. Volume should ideally be between 200 and 300 ml [13,14]. The optimal framing rate is between 15 and 30 s, and not 60 s, which leads to significant reflux being missed [15]. The lungs should be clear of tracer activity normally, apart from a small contribution from early absorption of DTPA into the blood pool and extravascular tissues. Computer modelling and clinical data indicate that as little as 0.1 MBq of activity aspirated into the lung can be detected by the gamma camera [16]. There is some conflict in the reported reproducibility measures of visual interpretation techniques compared with analysis of time–activity curves. In one series, the computerized analysis was significantly better [17] whereas in another, visual interpretation appeared more accurate [18].

The two key findings of the current study are the unexpected proportion of patients who proceed to aspirate refluxate into the lungs in both groups. There is a clear and significant difference in the rates of lung aspiration between the GERD and the LPR patients. Although relatively small at 11/80 (14%) cases in the GERD group and high in the LPR group [48/205 (23%)], the finding is nevertheless significant as this is silent lung aspiration. This may partly explain associated, but apparently unrelated, conditions such a bronchiectasis [19] and lung fibrosis (Fig. 4) resulting from acid aspiration into the lungs [20,21]. Increasing tracer activity in the upper oesophagus was predictive of lung aspiration in patients with symptoms of LPR. There was a good correlation between the activity in the upper oesophagus, pharynx and lung aspiration in both patient groups.

Unlike pH monitoring, scintigraphy can detect nonacid reflux. Unlike multichannel impedance, it is less likely to suffer interference from normal respiratory activities. However, it measures reflux more coarsely, has a relatively short sampling time and cannot provide detailed information on the number or the nature of reflux episodes. It does not adequately convey an idea of the severity of the disease that informs the appropriateness of surgical intervention. This is critical as there are data showing that as few as three episodes of LPR per week may lead to significant laryngeal inflammation and injury [22]. Therefore, on the basis of data available in this study, scintigraphy seems to be primarily useful as a litmus test for pulmonary aspiration, which can stratify the link and lead to more invasive studies such as 24-h impedance and pH studies.

This raises two obvious questions: Does the presence of aspiration on scintigraphy correlate with other known objective measures of LPR, such as proximal exposure on 24 h pH and/or impedance monitoring? Does aspiration on scintigraphy indicate that surgery or medical treatment is likely to be successful? Work that has been submitted recently for publication by our group in 34 patients with chronic cough and LPR who underwent laparoscopic fundoplication provides a partial answer to these questions. As this was a highly selected group of patients with severe LPR, the finding of aspiration on scintigraphy in 50% of cases is probably not surprising. The symptomatic response rate to surgery was over 90%, suggesting that lung aspiration is very likely to be an indication for surgery. Furthermore, it is known that cough can also be triggered by nonacid or even basic refluxate because of previous sensitization of the airways or by reflex mediation [23]. There is also the potential for progressive lung disease in patients who continue to aspirate while on medical therapy alone.

This study also raises a number of questions that require more careful study and consideration. There is a significant age difference (7.7 years) between the patients with GERD versus the group with LPR. This suggests a much longer natural history of the disease in patients with LPR, which reflects the delay in diagnosis. Clinical awareness of the potential for silent LPR is a key factor just as it is in patients with ostensible GERD alone who may also have silent LPR. Scintigraphy offers a rapid and noninvasive method of screening such patients. These issues, however, require a careful prospective study.

Two drawbacks of the study are the retrospective collection of data and the different reporting standards for reflux scintigraphy that have evolved throughout the lifetime of the technique. The patients underwent scintigraphy over a period of 8 years, and in that time, our group has developed new methods of semiquantification and reporting. A study in which patients were recruited prospectively and that made use of a more detailed standard reporting template would provide greater data integrity for analysis. This is currently under way at a number of centres, which will further test the integrity and reproducibility of the technique. The main strengths of the study are the standardized approach to scintigraphy during the current study and the consistent clinical approach. All scintigraphic studies were carried out through a single service following a single protocol. Patients' histories were assessed by a single senior clinician or their locum, and categorized as GERD or LPR according to a consistent, standardized format. These assertions are supported by a power of 0.7 for the study, with a low likelihood of type I or II errors.

Conclusion

A high level of pulmonary aspiration was identified in this carefully selected patient group with LPR symptoms. The clinical history failed to identify significant reflux or aspiration in a high proportion of patients. There appears to be a significant difference in the height of reflux identified in GERD versus LPR patients. LPR symptoms and scintigraphy are associated significantly with pharyngeal isotope exposure. This study provides evidence for scintigraphic reflux studies in playing a role as a screening test for suspected LPR or lung aspiration associated with GERD.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Dickman R, Kim JL, Camargo L, Green SB, Sampliner RE, Garewal HS, Fass R. Correlation of gastroesophageal reflux disease symptoms characteristics with long-segment Barrett's esophagus. *Dis Esophagus* 2006; **19**:360–365.

2 Fass R, Dickman R. Clinical consequences of silent gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2006; **8**:195–201.

3 Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. *Cleve Clin J Med* 2010; **77**:327–334.

4 Poelmans J, Tack J. Extraoesophageal manifestations of gastro-oesophageal reflux. *Gut* 2005; **54**:1492–1499.

5 Spechler SJ. Laryngopharyngeal reflux: a cause of faulty phonation or a faulted, phony diagnosis? *Clin Gastroenterol Hepatol* 2006; **4**:431–432.

6 Vaezi MF. Laryngitis and gastroesophageal reflux disease: increasing prevalence or poor diagnostic tests? *Am J Gastroenterol* 2004; **99**:786–788.

7 Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice* 2002; **16**:564–579.

8 Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol* 1993; **88**:25–29.

9 Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005; **100**:283–289.

10 Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. *Gastroenterology* 2008; **135**:756–769.

11 Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, *et al*. Groupe Franais De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; **11**:366–372.

12 Ang D, Ang TL, Teo EK, Hsu PP, Tee A, Poh CH, *et al*. Is impedance pH monitoring superior to the conventional 24-h pH meter in the evaluation of patients with laryngorespiratory symptoms suspected to be due to gastroesophageal reflux disease? *J Dig Dis* 2011; **12**:341–348.

13 Russell C. Functional evaluation of the esophagus. In: Hill L, editor. *The esophagus medical and surgical management*. Philadelphia: WB Saunders; 1988. p. 45.

14 Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. *Am J Gastroenterol* 1992; **87**:1094–1101.

15 Seymour JC, West JH, Drane WE. Sequential ten-second acquisitions for detection of gastroesophageal reflux. *J Nucl Med* 1993; **34**:658–660.

16 Ruth M, Carlsson S, Månsson I, Bengtsson U, Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. *Clin Physiol* 1993; **13**:19–33.

17 Caglar M, Volkan B, Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time–activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. *Nucl Med Commun* 2003; **24**:421–428.

18 Tuncel M, Kiratli PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. *World J Pediatr* 2011; **7**:245–249.

19 Piccione JC, McPhail GL, Fenchel MC, Brody AS, Boesch RP. Bronchiectasis in chronic pulmonary aspiration: risk factors and clinical implications. *Pediatr Pulmonol* 2012; **47**:447–452.

20 Lee JS, Collard HR, Raghu G, Sweet MP, Hays SR, Campos GM, *et al*. Does chronic microaspiration cause idiopathic pulmonary fibrosis? *Am J Med* 2010; **123**:304–311.

21 Raghu G. The role of gastroesophageal reflux in idiopathic pulmonary fibrosis. *Am J Med* 2003; **Suppl 3A** (Suppl 3A):60S–64S.

22 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991; **101** (Pt 2 Suppl 53):1–78.

23 Patterson RN, Johnston BT, Ardill JE, Heaney LG, McGarvey LP. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 2007; **62**:491–495.