Am J Nucl Med Mol Imaging 2020;10(6):342-348
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0123415

Original Article

Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers

Leticia Burton[1], Gregory Leighton Falk[2], John Beattie[3], Daniel Novakovic[4], Scott Simpson[5], Hans Van der Wall[1]

[1]CNI Molecular Imaging & University of Notre Dame, Sydney, Australia; [2]Sydney Heartburn Clinic, Concord Hospital & University of Sydney, Australia; [3]Eastwood, Sydney, Australia; [4]Department of ENT Surgery, Canterbury Hospital, Faculty of Medicine and Health, University of Sydney, Australia; [5]Section of Gastroenterology, Sydney Adventist Hospital, Sydney, Australia

Received September 29, 2020; Accepted October 6, 2020; Epub December 15, 2020; Published December 30, 2020

Abstract: Gastroesophageal reflux disease (GERD) is a common and growing problem in most western countries. It may present with the typical symptoms of heartburn and regurgitation or with the effects of extra-esophageal disease. We have developed and validated a scintigraphic test that evaluates reflux at both sites in patients at high risk of laryngopharyngeal reflux and lung aspiration. We hypothesized that the test may be able to separate physiologic reflux from pathological reflux and examined this possibility in normal asymptomatic volunteers. Asymptomatic volunteers were screened with the Belafsky reflux symptom index (RSI) and entered into the trial if scores were less than 13. ^{99m}Tc Phytate was ingested orally and dynamic studies from the pharynx to the stomach were obtained while upright and supine. A delayed study of the thorax was also obtained for lung aspiration of refluxate. Studies were semi-quantitated graphically as time-activity curves. A total of 25 volunteers were studied (13 M, 12 F) with a mean age of 57.5 yr (Range 40-85 yr). None gave a history of heartburn or regurgitation. Mean RSI was 4.1 (range 0-10). Testing showed upright gastroesophageal reflux to the mid-upper esophagus without pharyngeal contamination in 32%. None of the subjects showed supine reflux or lung aspiration. This result corresponds well with intraluminal impedance/pH monitoring in normal volunteers. The scintigraphic reflux test gives similar results to standard intraluminal impedance/pH studies in normal volunteers. A significant proportion of asymptomatic volunteers demonstrate upright reflux only.

Keywords: GERD, gastroesophageal reflux disease, scintigraphy, normal volunteers, asymptomatic, upright reflux

Introduction

Gastroesophageal reflux disease (GERD) is common [1] with a growing prevalence in Western society [2]. The increasing prevalence has been linked to obesity [3] which in itself is linked to an increased prevalence of diabetes mellitus [4, 5]. This triad of diseases contributes to the overall increase in chronic disease, which has been estimated to reach $US10.059 Trillion by 2022, an annual growth rate of 5.4% [6].

It has been estimated that approximately 45% of the population in most western countries suffers from GERD [7]. GERD is a condition that is characterised by the symptoms of heartburn and regurgitation [8]. However, the extra-esophageal manifestations of GERD are less well understood, particularly laryngopharyngeal reflux (LPR) [9]. The symptoms of LPR include throat clearing, persistent cough, globus pharyngeus, and dysphonia. Unfortunately, the diagnosis of LPR has been quite difficult, with recent work indicating that intraluminal esophageal impedance studies utilising a pharyngeal electrode may help to establish the diagnosis, although the technique remains in question due to interobserver variability [10]. Furthermore, there is a significant overlap of GERD and LPR symptomatology, although many of the symptoms of LPR are often overlooked [11]. There is clearly potential for a simple test that can demonstrate LPR and lung aspiration of refluxate with some degree of certainty.

A relatively simple scintigraphic test for the detection of gastroesophageal reflux disease at

Table 1. LARYNGO-PHARYNGEAL REFLUX SYMTPOM INDEX

Symptom	0	1	2	3	4	5
Hoarseness or a problem with your voice						
Clearing your throat						
Excess throat mucous or postnasal drip						
Difficulty swallowing foods, liquids, or pills						
Coughing after you eat or after lying down						
Breathing difficulties or choking episodes						
Troublesome or annoying cough						
Sensations or something sticking in your throat or a lump in your throat						
Heartburn, chest pain, indigestion, or stomach acid coming up						

Within the last month, how did the following problems affect you? (0= No problem to 5= severe problem).

the level of the esophagus and in the extra-esophageal structures such as the laryngo-pharynx and lungs has been developed and validated [12, 13]. As sulfur colloid is no longer available in Australia, the replacement agent, ^{99m}Tc Phytate is currently in use for gastro-esophageal studies such as reflux and gastric emptying. The current study presents the application of the scintigraphic test to a group of normal (asymptomatic) subjects in order to assess the background rate and pattern of physiological gastroesophageal reflux and any characteristics that distinguish it from pathological reflux.

Materials and methods

Subject demographics

Volunteers (≥ 40 years of age) were screened for symptoms of gastroesophageal reflux disease with questions regarding heartburn, regurgitation and globus etc. The reflux symptom index (RSI) of Belafsky et al. [14] was also administered. Nine symptoms pertaining to reflux are graded from 0 (none) to 5 (most severe) and the sum of these scores is the reflux symptom index. The relevant criteria are shown in **Table 1** [14]. Subjects with an RSI score above 13 were excluded from the study. Other exclusion criteria included pregnancy, history of abdominal surgery, asthma or known lung disease.

Ethical considerations

The study was approved by the institutional ethics committee of the University of Notre Dame, Sydney Campus (Reference number 015149S). In adherence to Human Research Ethics Committee (HREC) guidelines all patients were provided with a Participant Information Sheet which outlined the project, risks involved and intended outcomes of the study. Written consent was obtained from all subjects. The use of ionising radiation requires extra provisions to be imposed. This is outlined in the Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes published by the Australian Radiation Protection Safety Agency. The code imposes restrictions that subjects not be under the age of 40 years, but where practical under the age of 50 years.

The dose estimate was extrapolated from the data published in the Knight et al. paper which calculated the effective dose for non-nutrient liquid gastric emptying studies [15].

In accordance with ethics approval the dose, was calculated by a qualified Radiation Safety Officer, who utilised the International Commission on Radiological Protection (ICRP) guidelines to estimate the effective dose to the patient. In optimising patient exposure, ^{99m}Tc Phytate is considered the ideal agent given its characteristic of not crossing the mucosal barrier of the stomach. The radiation exposure of the ^{99m}Tc Phytate for the administered mean dose of 60 MBq was estimated at 0.97 mSv [15].

Scintigraphy

Subjects were fasted for 6 hours prior to the test. A dose of 60-70 MBq of ^{99m}Tc Phytate was administered in 50 mL of water followed by a further 50 mL of water to clear the oro-pharynx and esophagus. Dynamic images were acquired upright for 2 minutes then supine

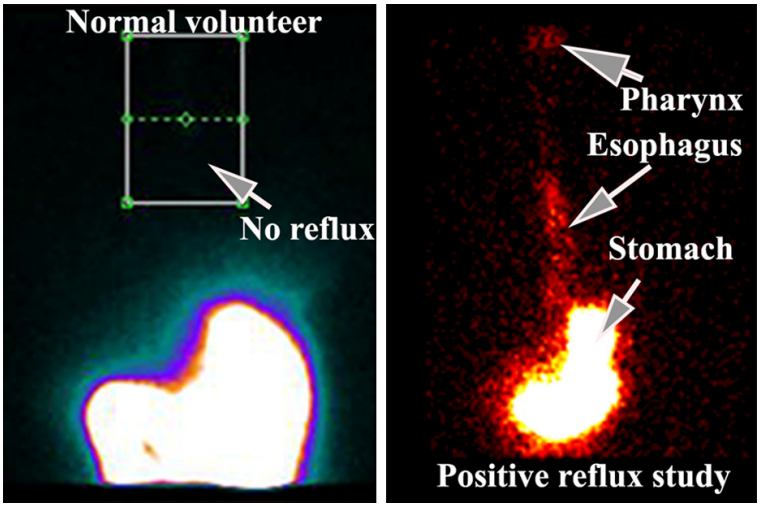

Figure 1. Summed image of frames from a supine study in a normal subject. There is no evidence of significant activity within the esophagus. Compare this with a dynamic study from a patient with symptomatic GERD, where there is significant reflux to the level of the oropharynx and activity visualised within the oesophagus. There is no other activity within the thorax thus identifying that any activity visualised is within the oesophagus and occasionally will be due to immediate aspiration of refluxate into the lungs. The central region of interest is placed just above the penumbra of scatter from the stomach activity. This is the initial step of analysis of the study and is useful for showing subtle reflux.

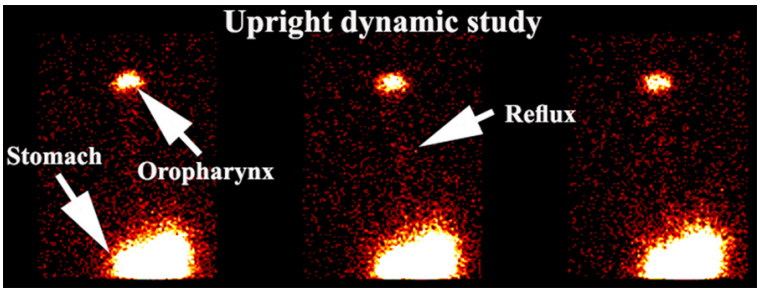

Figure 2. The sequence of dynamic images from the upright study demonstrates subtle reflux to the level of the upper esophagus in a normal volunteer. There is moderate retention of activity in the oropharynx from the initial tracer administration. One of the important technicalities is to place the region of interest below the oropharyngeal activity in order to capture the signal from the laryngopharyngeal region.

for 30 minutes on a Hawkeye 4 hybrid gamma camera (General Electric, Milwaukee, United States) with the mandible and stomach in the field of view (**Figures 1** and **2**). Delayed static imaging was obtained 2 hrs later for assessment of lung aspiration of refluxate. Image analysis is shown in **Figures 3** and **4**. Time-activity curves were obtained for the pharynx/laryngopharynx, upper esophagus and background. Background subtracted curves were obtained for the pharynx/laryngopharynx and upper esophagus. A ratio of the curves for pharynx/laryngopharynx to background was obtained. Liquid gastric emptying was calculated by an exponential fit to the time-activity curve for the stomach. The only structures visualized in the scintigraphic studies are activity in the pharynx/laryngopharynx, esophagus and the stomach. No other organs are visualised until acquisition of the late study which may show activity in the lungs as the scintigraphic agent does not cross the mucosal barrier and there is no significant background activity other than scatter from the stomach.

Statistics

All statistical analysis was obtained with the Statistical Package for the Social Sciences (SPSS) Version 24 (IBM, New York, USA).

Results

Subject demographics

The study group of 25 subjects was comprised of 13 males and 12 females with a mean age of 57.5 years (SD 12.7, Range 40-85 years). None gave a history of heartburn, regurgitation or chronic cough. The mean Belafsky RSI score was 4.1 (Median 4.0, SD 3.6, Range 0-10). Three other subjects were excluded as the scintigraphic scans showed significant GERD when supine and subsequent investigations (pH/impedance and manometry) confirmed disease, although the Belafsky RSI scores were below 13 (silent LPR). These three subjects had findings consistent with LPR on subsequent laryngoscopy.

Scintigraphic scan findings

Eight of 25 subjects (32%) demonstrated gastroesophageal reflux to the mid-upper esophagus when upright which did not reach the pharynx (**Figure 2**). No subject had supine reflux or

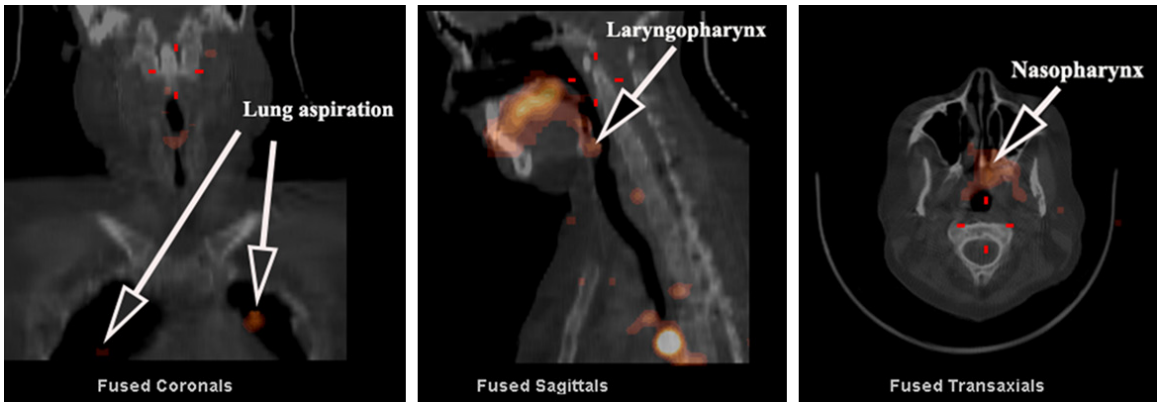

Figure 3. Abnormal patient study. The fused SPECT/CT images of the head, neck and chest demonstrate evidence of refluxate contaminating the oropharynx, laryngopharynx, and nasopharynx. There is also evidence of aspiration of refluxate into the lungs. These studies are routinely acquired in the patient studies. This could not be done with the asymptomatic volunteers due to restrictions of radiation exposure. It provides good orientation of the anatomy when the functional images are fused with the low-dose CT, allowing visualisation of hiatus hernias and possible compression of the cardiac structures.

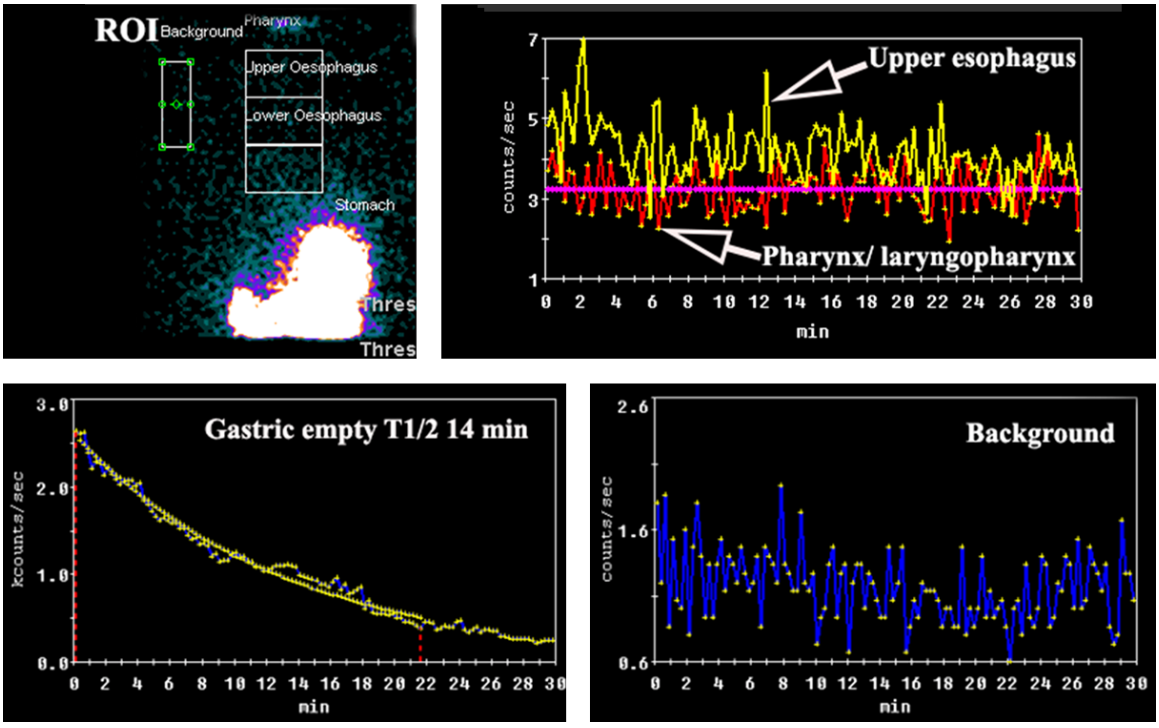

Figure 4. Analysis of supine images. This is a dynamic study obtained for 30 minutes. ROI demonstrates the regions of interest and background over the right lung. The time-activity curves for the pharynx/laryngopharynx (red) with the fitted curve (pink) and the upper esophageal curve (yellow) is shown in the top right panel. Liquid gastric emptying time is shown in the lower left panel. Background activity is illustrated in the lower right panel. Various numeric indices can be derived from these curves.

evidence of aspiration into the lungs in the delayed study.

Analysis of the scintigraphic studies showed no evidence of a rising time-activity curve for the pharynx/laryngopharynx or upper esophagus. Most curves showed a declining pattern with a minority having a flat pattern (n=4). The analysis of the ratio of area under the curve for pharynx/laryngopharynx to background was a me-

an of 1.1 (Median 1.1, SD 0.59, Range 0.10-1.70). The mean amplitude for the pharyngeal/laryngopharyngeal to background curve was 1.2 (Median 1.6, SD 1.1, Range 0-2.3).

There was no significant correlation between subjects with upright gastroesophageal reflux and the RSI ($p>0.05$).

Liquid gastric emptying was a mean of 6.5 minutes (Median: 6.8, SD: 3.4, Range: 1.0-10.0).

The radiation exposure of the ^{99m}Tc Phytate for the administered mean dose of 60 MBq was estimated at 0.97 mSv [15].

Discussion

The findings of upright reflux in 32% of asymptomatic volunteers which does not reach the pharynx is similar to the results of 24-hour ambulatory intraluminal esophageal impedance and pH monitoring in healthy volunteers [16]. In that study, a median of 34% of upright reflux reached the proximal esophagus with acid reflux being twice as common as weakly acidic reflux. This also illustrates the findings previously reported, whereby reproducibility is adversely affected at RSI scores <13, as no patient who demonstrated upright reflux had an abnormal RSI score [17].

The scintigraphic test provides visualisation of reflux in the esophagus in the early dynamic studies and allows an assessment of the maximal level of the reflux episodes (**Figure 2**). With appropriate quantification, one can enumerate these findings (**Figures 3** and **4**). Most importantly, the pH of the refluxate is of no relevance to the degree or extent of reflux as it is a purely functional phenomenon of tracer in water that demonstrates the relevant pathophysiology. Hence the ability of the test to provide visualisation of acidic or basic refluxate, which becomes important in the detection of reflux in patients on maximal antacid therapy or with weakly acidic or alkaline reflux, as often happens in cases of LPR [18].

Physiological upright gastroesophageal reflux is common for a number of reasons. Combined intraluminal esophageal manometry and pH studies in normal volunteers has shown that the lower esophageal sphincter (LES) is more competent when supine than upright [19]. This occurs even when the resting lower esophageal sphincter pressure is normal. The study also showed that physiologic reflux is unaffected by age, is generally asymptomatic and of short duration. It mostly occurs after meals and rarely during sleep. Upright reflux is rapidly cleared by swallowing. The sequence of observations suggests that factors other than gravity influence reflux in the upright position. One could hypothesize that when upright the gastric air bubble moves into the fundus and may induce a venting reflex with a resultant fall in LES pressure. It has been suggested that the air bubble in the fundus may stimulate mechanoreceptors that lead to transient lower esophageal sphincter relaxations, permitting intermittent reflux [20-23]. Demeester et al. [19] did note a much higher incidence of burping in these patients in support of this hypothesis. Comparative manometric measurements between the upright and supine position in normal volunteers has also shown a mean pressure drop of 12 mmHg between the stomach and mid-esophagus when upright [24].

This scintigraphic reflux study is critically dependent on close attention to technical details. The volume of fluid introduced into the stomach is important, as distension by large volumes can induce reflux. Such a phenomenon has been shown to be due to an increase in transient lower esophageal sphincter relaxations as stomach volumes increase from 250 to 500 mL [25]. While smaller volumes may underestimate the degree of reflux, the literature suggests that optimal results are obtained with approximately 150 mL of fluid [26, 27]. Sampling rates for the dynamic studies are also critical. Earlier experience with 60 second sampling found significant degrees of reflux could be missed and more appropriate sampling times have been shown to be in the vicinity of 15 seconds per frame [28]. This does not diminish the ability to detect reflux events as images can be summed together for qualitative assessment (**Figure 1**).

The quantification of the reflux studies has elicited mixed results in the past, with some authors finding it to be helpful [29] and others showing it to be inferior to visual interpretation [30]. We have found it to be helpful as time-activity curves can be utilised to assess the time to clear the esophagus and pharynx/laryngopharynx of refluxate (rising versus declining curves and the ratio of area under the curve for pharynx/laryngopharynx to back-

ground indicating the delay in clearance with rising ratios). One has to be careful with placement of the regions of interest in order to avoid any retained activity in the oropharynx contaminating the data. The top of the region of interest must be placed below the oropharynx in order to include the inferior part of the pharynx and the laryngopharynx (See **Figure 2**). The spikes of increased activity in the time activity curves may be helpful in indicating the frequency of reflux and provide an estimate of the volume of reflux from the amplitude measures (**Figure 4**). These variables have been shown to correlate with intraluminal esophageal impedance/pH studies [31]. Findings in this study showed an amplitude and area under the curve ratio for pharynx/laryngopharynx that was close to 1, indicating it approximated background readings. None of the time-activity curves showed a rising pattern indicative of progressive reflux and/or an impaired clearance mechanism.

The issue of noise, especially related to the small dose of tracer used in the study (~100 MBq) is less of a problem than in other scintigraphic studies as the background level of activity in the thorax is relatively low as there is generally no systemic absorption and the principal contributor is scatter from activity in the stomach. Images can be scatter-corrected to overcome this problem. This is more likely to affect the lower third of the esophagus than the laryngopharyngeal and upper esophageal regions of interest. Poisson noise can be handled by filtering. The consistency of the time-activity curves for the pharyngeal/laryngopharynx and upper esophagus can also distinguish random noise from spikes of activity within the esophagus by the consistency of occurrence in the temporal domain. Modelling has demonstrated that as little as 0.1 MBq can be detected in the lungs, increasing the level of confidence for detection of aspiration of refluxate as there is no significant activity in the lung other than scatter from the stomach [32]. Scatter correction can significantly reduce this activity as well.

Conclusions

This study in normal volunteers has shown that approximately one third of asymptomatic patients have scintigraphically evident gastroesophageal reflux when upright. None of the "normals" demonstrated reflux when supine. No contamination of the pharynx or lungs by refluxate was demonstrated in the normal subjects. Such findings accord well with the large multi-centre trial in normal volunteers utilising intraluminal impedance/pH studies. The scintigraphic study has a low radiation dose, is simple to perform and well tolerated. Although simple, the scintigraphic study requires careful attention to detail in terms of the methodology and technicalities. Appropriate quantification is important in order to maintain fidelity of the technique.

Disclosure of conflict of interest

None.

Address correspondence to: Hans Van der Wall, CNI Molecular Imaging & University of Notre Dame, Suite 101, 5 Bay Drive, Meadowbank, NSW 2114, Sydney, Australia. Tel: +61 2 9736 1040; Fax: +61 2 9736 2095; E-mail: hvanderwall@gmail.com

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