Enterogastric Bile Reflux during Technetium-99m-Sestamibi Cardiac Imaging

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Enterogastric bile reflux (EGBR), a risk factor for both gastritis and esophagitis, is a potentially treatable noncoronary cause for chest pain. **Methods:** To investigate the frequency of EGBR during different ^{99m}Tc-sestamibi cardiac imaging, 1405 consecutive ^{99m}Tc-sestamibi SPECT myocardial perfusion studies were reviewed. **Results:** One hundred sixteen of the 1405 patient studies (8.3%) showed EGBR with roughly equal numbers of patients having marked (43 patients), moderate (38 patients) or minimal (35 patients) intensity of abnormal gastric activity. Two examinations showed gastroesophageal reflux of activity. EGBR was less frequent with treadmill stress testing (5.5% patients) than with pharmacologic stress testing using either dipyridamole (11% of patients) or dobutamine (9.2% of patients) ($p > 0.005$). EGBR also was more frequent in patients over 40 yr of age. Finally, the prevalence of upper gastrointestinal symptoms and the frequency of established upper gastrointestinal diagnoses correlated strongly with the presence and intensity of EGBR. **Conclusion:** Clarification of the full clinical significance of EGBR during ^{99m}Tc-sestamibi cardiac imaging is a topic for future research. Nonetheless, the imaging finding of EGBR may, in fact, identify a potentially treatable noncoronary cause for chest pain.

Key Words: technetium-99m-sestamibi; cardiac abnormalities; esophagitis; gastritis; SPECT; myocardial imaging

J Nucl Med 1996; 37:1285–1288

Enterogastric bile reflux (EGBR) is a risk factor for both gastritis and esophagitis (*1–5*). EGBR occurring during ^{99m}Tc-sestamibi cardiac imaging has previously been documented as a cause for imaging artifacts (*6,7*). Furthermore, previous studies have demonstrated that esophageal pain may be indistinguishable from the pain of ischemic coronary artery disease (*8–15*). It is tempting to speculate that the finding of EGBR during ^{99m}Tc-sestamibi cardiac imaging may also identify a potentially treatable noncoronary cause for chest pain.

For patients studied with myocardial perfusion imaging as part of a coronary artery disease evaluation, 8% to 11% of the intravenously injected dose of ^{99m}Tc-sestamibi typically is excreted in the bile. This activity, which is greater than the approximately 5% of the injected dose typically concentrated in the heart during a normal study, allows for visualization of the liver, bile ducts and loops of bowel which normally receive bile flow. In addition, the activity is more than sufficient to identify EGBR. In fact, similar hepatobiliary techniques using ^{99m}Tc-Disida or ^{99m}Tc-Hida have previously been studied as methods for demonstrating EGBR (*16–20*). During ^{99m}Tc-sestamibi SPECT cardiac studies, the stomach, duodenum, common bile duct and most of the liver are routinely included in the field of view on the projection images. At our institution, 32 projection images over 180° of rotation of a 400-mm gamma camera are acquired during these studies. Thus, a series of 32 rotating planar images which depicts any EGBR are routinely available for review as part of SPECT myocardial perfusion imaging studies. To investigate the frequency of EGBR, a retrospective review of these planar projection images from ^{99m}Tc-sestamibi SPECT myocardial perfusion studies was undertaken.

Received May 25, 1995; revision accepted August 18, 1995.

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MATERIALS AND METHODS

The imaging data and medical records for 1405 consecutive adult patients with known or suspected coronary artery disease referred for SPECT myocardial perfusion imaging between November 1, 1992 and June 31, 1994 were reviewed. The population consisted of 732 men and 673 women with a mean age of 57 yr (age range 19–89 yr). All patients underwent either treadmill or pharmacologic stress/rest myocardial perfusion imaging using a one-day ^{99m}Tc-sestamibi protocol. Stress testing was performed using symptom-limited treadmill exercise in 653 patients, dipyridamole pharmacologic stress in 611 patients and dobutamine pharmacologic stress in 141 patients.

For treadmill stress, a symptom-limited exercise test was performed using the standard Bruce protocol. Treadmill exercise was terminated due to fatigue, chest pain, dyspnea, arrhythmia or ischemic ECG changes. Heart rate, blood pressure and 12-lead ECG were recorded. Dipyridamole pharmacological stress testing was performed using a 4-min infusion of 0.142 mg/kg/min dipyridamole. Dobutamine pharmacologic stress testing was performed in a graded stepwise fashion starting with a low dose (5 μg/kg/min) and increasing the dose as tolerated every 5 min up to 40 μg/kg/min. Atropine (0.2–0.4 mg boluses every 2 min up to a total dose of 2.0 mg) was infused as needed to achieve 85% of age-predicted maximum heart rate. End points for pharmacologic stress testing were maximum dose, target heart rate, clinical ischemia, arrhythmia, hypertension or hypotension. Heart rate, blood pressure and 12-lead ECG were recorded.

Same-day stress/rest ^{99m}Tc-sestamibi SPECT imaging was performed using our institution's standard protocol. Stress and rest images were acquired 1 hr after injecting 370 MBq (10 mCi) and 1100 MBq (30 mCi) of ^{99m}Tc-sestamibi, respectively. All patients were encouraged to eat a fatty meal to promote bile flow and increase the liver and gallbladder clearance of activity. SPECT was performed by acquiring 32 projections over 180° (from 45° RAO to 45° LPO) on a circular, 400-mm field of view gamma camera. All data were stored in 64 × 64 matrices. Acquisition time per projection was 40 sec and 20 sec for stress and rest studies, respectively. To provide a permanent imaging record, all 32 planar projection images from both the stress and rest studies were photographed along with the reconstructed SPECT images. The planar projection images are used clinically to document any patient movement and evaluate extra-cardiac radiopharmaceutical uptake.

For this research project, the films showing both SPECT and planar projection images for all 1405 patients were evaluated

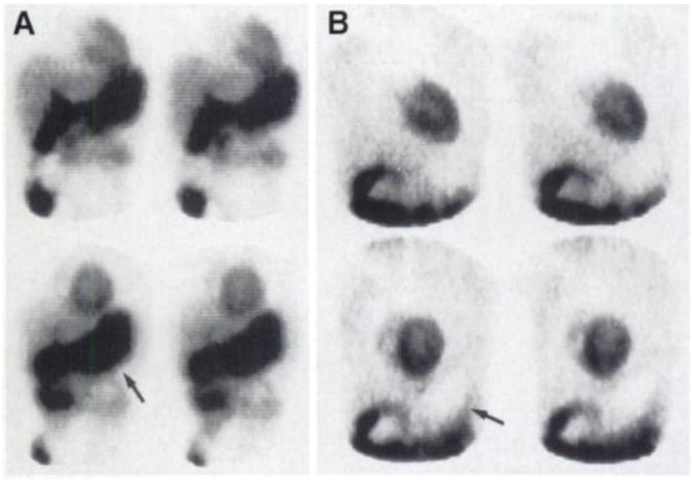

FIGURE 1. Marked enterogastric bile reflux in a 53-yr-old man with chest pain. Four projection images from a treadmill stress ^{99m}Tc-sestamibi SPECT study show (A) marked activity in the stomach (arrow) greater in intensity than myocardial uptake. A study 1 yr earlier (B) showed the stomach as a relatively photon-deficient area (arrow) with no evidence of EGBR.

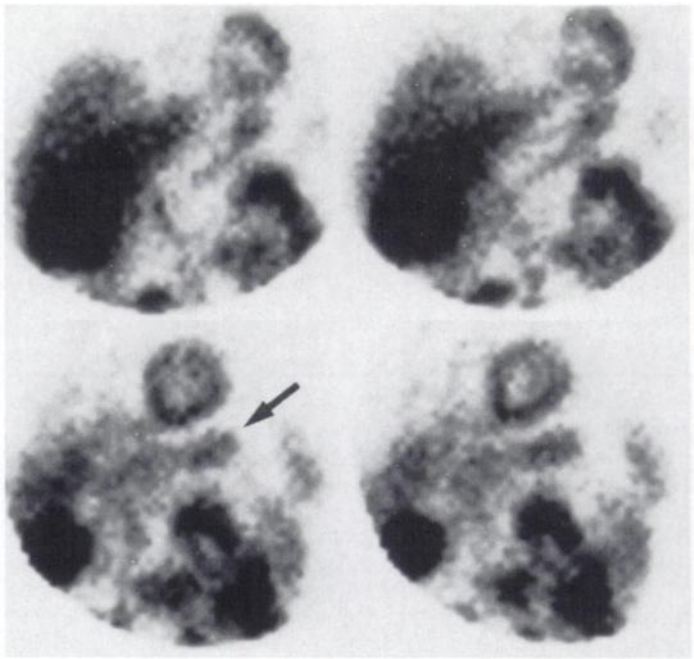

FIGURE 2. Moderately intense enterogastric bile reflux in a 53-yr-old man with coronary artery disease previously treated by angioplasty. Four images from a dipyridamole pharmacologic stress ^{99m}Tc-sestamibi SPECT study show moderately intense activity in the stomach (arrow) equal intensity to the myocardial uptake.

retrospectively by two nuclear medicine physicians working together. Scans were scored as positive for EGBR only if the two physicians agreed on the presence of EGBR. Radioactivity in the stomach was accepted as evidence of EGBR and scored based on intensity as being marked (more intense than the heart), moderate (equal in intensity to the heart) or minimal (less intense than the heart).

For the 116 patients with evidence of EGBR, 103 complete medical records were available for review. These 103 medical records, in addition to the medical records of 28 randomly selected ^{99m}Tc-sestamibi patients (mean age 59 yr) without evidence of EGBR, were reviewed to document any established diagnosis of gastrointestinal disorders and any symptoms of upper gastrointestinal disease (e.g., pain or heartburn relieved by antacids, regurgitation and aspiration). Any established diagnosis of upper gastrointestinal disease documented by endoscopy, radiography or surgery also was recorded.

Statistical analysis was performed using the chi square test; results with $p < 0.05$ were considered statistically significant.

RESULTS

EGBR was observed in 116 of the 1405 patients (8.3%) with roughly equal numbers of patients having marked (43 patients), moderate (38 patients) and minimal (35 patients) gastric activity. Of the 116 patients with EGBR, 14 had prior gastric surgery placing them at higher risk for EGBR. Figure 1 demonstrates marked activity in the stomach greater in intensity than the activity seen in the heart. Figure 2 demonstrates moderately intense gastric activity roughly equaling the intensity of activity in the heart. For 57% of patients with EGBR gastric activity was demonstrated on both stress and rest images. Furthermore, for 12% of such patients, EGBR was seen only on the stress study while for 31% EGBR was present only on the resting study. As shown in Table 1, EGBR was less frequent with treadmill stress testing (36 of 653 patients or 5.5%), than with pharmacologic stress testing using either dipyridamole (67 of 611 patients or 11.0%) or dobutamine (13 of 141 patients or 9.2%) ($p < 0.005$). For two patients, gastroesophageal bile reflux also was demonstrated (Fig. 3).

Technetium-99m-sestamibi SPECT myocardial perfusion studies were classified as either normal (49% of patients), abnormal with one or more fixed perfusion defects (19% of patients) or abnormal with one or more reversible perfusion defects (32% of patients). EGBR was randomly distributed among the patients in these three myocardial perfusion categories, suggesting that the frequency of EGBR was independent of the distribution of hemodynamically significant coronary artery disease in this patient population.

The frequency of EGBR was slightly higher in men (9.3%) than in women (7.0%) although this difference was not statistically significant. Furthermore, as is shown in Table 2, EGBR occurred in only 2 of the 104 subjects under 40 yr of age but was significantly more frequent in subjects over 40 yr of age ($p < 0.01$).

Table 3 shows the frequency of upper gastrointestinal symptomatology and of established diagnoses of upper gastrointestinal disease both for 103 patients with EGBR and for 28 patients without evidence of bile reflux. Established diagnoses included peptic ulcer disease (32 patients), hiatal hernia (12 patients), esophageal dysfunction including esophagitis (14 patients) and gastritis (5 patients). There was a total of 77 instances of upper gastrointestinal pathology documented by endoscopy, radiography or surgery, with several patients having more than one condition. Note that when progressing from minimal EGBR through moderate and on to marked bile reflux there is an increase in the prevalence of upper gastrointestinal symptoms and the frequency with which a diagnosis of upper gastrointestinal disease has been established ($p < 0.01$). In

TABLE 1
Frequency and Severity of Enterogastric Bile Reflux in 1405 Patients

Severity of EGBR	Treadmill stress	Dipyridamole	Dobutamine	Total
Minimal	11	22	2	35
Moderate	10	23	5	38
Marked	15	22	6	43
Total patients	36 of 653 (5.5%)	67 of 611 (11.0%)	13 of 141 (9.2%)	116 of 1405 (8.3%)

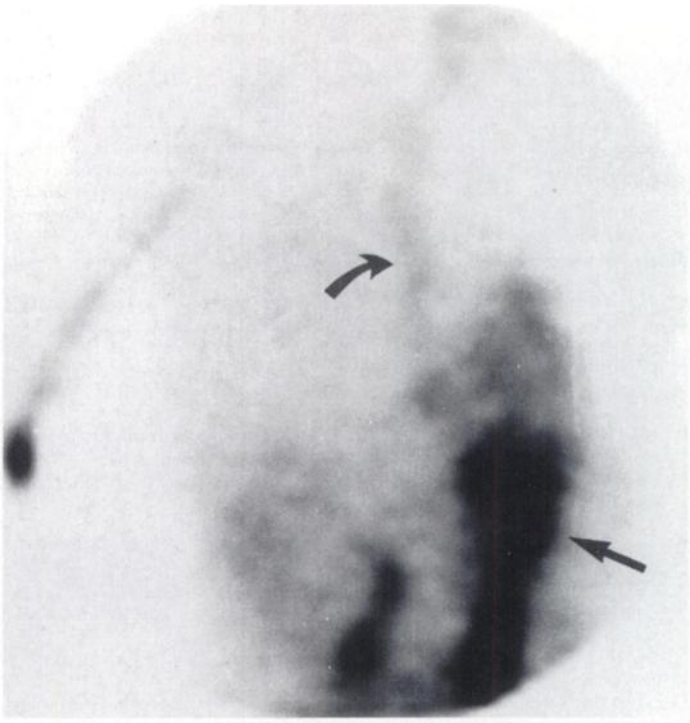

FIGURE 3. Gastroesophageal bile reflux in a 50-yr-old woman with prior surgical history of gastrojejunostomy for peptic ulcer disease. The patient now complains of chest pain and heartburn. RAO image from dipyridamole ^{99m}Tc-sestamibi SPECT study shows activity throughout the esophagus (curved arrow). In addition, marked activity due to EGBR is seen in the stomach (straight arrow).

particular, among 38 patients with marked EGBR 74% suffered from upper gastrointestinal symptoms and 50% had an established diagnosis of upper gastrointestinal disease. There is a statistically significant difference when this marked EGBR group is compared with the group of 28 patients without EGBR of whom only 43% suffer from upper gastrointestinal symptoms and only 29% had an established diagnosis of upper gastrointestinal disease ($p < 0.01$).

DISCUSSION

As many as 20% of patients with angina-like chest pain undergoing cardiac catheterization are found to have angiographically-normal coronary arteries (*21–24*). In addition, some patients with ischemic coronary artery disease, despite receiving optimal anti-anginal therapy, continue to experience severe chest pain (*13*). To treat these symptomatic patients, selective use of anti-acid therapy with H2-blockers has been advocated (*9,12–15*). Such treatment has been directed principally toward esophageal dysfunction, although the best method of identifying patients with noncardiac chest pain who respond to such anti-acid therapy is not established (*15*). Methods of selecting patients which have been advocated include esophageal manometry, acid perfusion testing, edrophonium challenge and 24-hour esophageal pH monitoring (*25–28*). The current retrospective review of EGBR in cardiac patients undergoing ^{99m}Tc-sestamibi SPECT myocardial perfusion imaging is an initial attempt at evaluating scintigraphic evidence of EGBR as a risk factor for treatable noncardiac chest pain.

TABLE 2
Frequency of Enterogastric Bile Reflux by Age in 1405 Patients

Age (yr)					
<30	30–39	40–49	50–59	60–69	>69
0 of 15 0%	2 of 89 2.3%	25 of 304 8.2%	34 of 382 8.9%	28 of 358 7.8%	27 of 257 10.5%

TABLE 3
Frequency of Upper Gastrointestinal Symptoms and Documented Upper Gastrointestinal Disease in Patients with and without Enterogastric Bile Reflux

	GI symptoms	GI disease
Minimal EGBR (34 patients)	18 (53%)$^{+}$	7 (21%)$^{+}$
Moderate EGBR (31 patients)	14 (45%)	9 (29%)
Marked EGBR (38 patients)	28 (74%)$^{*+}$	19 (50%)$^{*+}$
Total with EGBR (103 patients)	60 (58%)	35 (34%)
Without EGBR (28 patients)	12 (43%)*	8 (29%)*

$^{*}p < 0.01$.
$^{+}p < 0.01$.

There is reason to believe that cardiac patients with EGBR undergoing medical therapy for coronary artery disease are at higher risk of developing esophageal dysfunction. It is known that certain calcium-channel blockers lower the tone of the lower esophageal sphincter (*29–31*). This in turn leads to more frequent reflux of bile-laden gastric contents into the esophagus. It has been demonstrated that gastroesophageal bile reflux is associated with esophagitis and esophageal dysfunction (*1–5*).

In the current study, EGBR was observed in 8.3% of patients. Older patients and patients undergoing pharmacologic as opposed to treadmill testing were significantly more likely to have EGBR on their imaging studies. Neither gender nor stress-induced left ventricular myocardial ischemia (defined as one or more reversible ^{99m}Tc-sestamibi perfusion defects) correlated with the imaging finding of EGBR.

For 103 of the 116 patients with EGBR, complete medical records were available for review. Medical records for 28 other patients in the series without EGBR were reviewed for comparison. The prevalence of upper gastrointestinal symptoms and frequency of established diagnosis of upper gastrointestinal disease is greatest for the patients with marked EGBR being approximately twice that of patients without evidence of EGBR. Preliminary results thus establish a rough correlation between the severity of EGBR and upper gastrointestinal dysfunction. However, a cause-and-effect relationship between EGBR and noncardiac chest pain cannot be established by this retrospective study. It is also not known how often EGBR during these ^{99m}Tc-sestamibi cardiac studies will occur in normal, asymptomatic populations. Using either ^{99m}Tc-disida or ^{99m}Tc-hida in conjunction with imaging techniques specifically designed to detect any EGBR, researchers previously have investigated the scintigraphic diagnosis of EGBR comparing results with endoscopy and 24-hr gastric pH monitoring (*17–20*). Most investigators have found that 24-hr gastric pH monitoring is superior to scintigraphic techniques in identifying EGBR as a cause of foregut symptoms (*17,19,20*). In addition, EGBR was demonstrated in up to 18% of asymptomatic normal volunteer subjects (*14,15,17*). Note, however, that these same series used cholecystokinin stimulation and imaging for up to 90 min to detect EGBR in as many as 18% of normal subjects. Among symptomatic patients undergoing such optimized scintigraphic studies, up to 53% had EGBR.

To establish the potential use of the ^{99m}Tc-sestamibi scintigraphic techniques performed with treadmill or pharmacologic stress testing in identifying EGBR as a cause for chest pain, a prospective study which includes both patients with noncoronary chest pain of upper gastrointestinal origin and asymptom-

atic controlled subjects would be needed. Such a study would be clinically relevant. A high percentage of patients with angina-like pain due to esophageal dysfunction will respond to antacid therapy (*15*). However, in view of the limitations of current methods for predicting which patients will respond to H-2 blockers and other anti-reflux therapy, Stahl has recently pointed out that the best method for identifying such patients remains unknown (*15*). In particular, some patients with non-cardiac chest pain in whom an empiric therapeutic trial fails may still have reflux-related chest pain. Furthermore, esophageal studies including esophageal manometry, acid perfusion testing, edrophonium challenge and 24-hr esophageal pH monitoring, are "insensitive methods of determining which patients will respond to aggressive anti-reflux therapy" according to Stahl. Thus, while further research is needed, it is tempting to speculate that the scintigraphic finding of marked EGBR during ^{99m}Tc-sestamibi cardiac imaging studies may identify a potentially treatable noncoronary cause for chest pain.

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Erratum

In the case report, "Gallium-67 Imaging of Pericardial Lymphoma in AIDS," by Prvulovich et al. (June issue of *JNM*, pages 995–996), the administered dose of gallium in the section, Indications for Gallium Scintigraphy, was printed incorrectly. The correct dose was **120 MBq (3.2 mCi)** and not 20 MBq (3.2 mCi).