Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.1764

World J Gastroenterol 2009 April 14; 15(14): 1764-1768
World Journal of Gastroenterology ISSN 1007-9327

BRIEF ARTICLES

Prevalence of linked angina and gastroesophageal reflux disease in general practice

Hirohito Kato, Takamasa Ishii, Tatsuo Akimoto, Yoshihisa Urita, Motonobu Sugimoto

Hirohito Kato, Takamasa Ishii, Tatsuo Akimoto, Yoshihisa Urita, Motonobu Sugimoto, Department of General Medicine and Emergency Care, Toho University School of Medicine, Omori Hospital, 6-11-1, Omori-Nishi, Ota-Ku, Tokyo 143-8541, Japan

Author contributions: Kato H and Ishii T collected all the human material and performed the majority of data collection; Akimoto T and Sugimoto M provided analytical tools and were also involved in editing the manuscript; Kato H and Urita Y designed the study and wrote the manuscript.

Correspondence to: Dr. Yoshihisa Urita, Department of General Medicine and Emergency Care, Toho University School of Medicine, Omori Hospital, 6-11-1, Omori-Nishi, Ota-Ku, Tokyo 143-8541, Japan. foo@eb.mbn.or.jp

Telephone: +81-3-37624151 Fax: +81-3-37656518
Received: January 5, 2009 Revised: February 16, 2009
Accepted: February 23, 2009
Published online: April 14, 2009

Abstract

AIM: To evaluate the association between gastroesophageal reflux diseases (GERD) and coronary heart diseases.

METHODS: One thousand nine hundred and seventy consecutive patients who attended our hospital were enrolled. All of the patients who first attend our hospital were asked to respond to the F-scale questionnaire regardless of their chief complaints. All patients had a careful history taken, and resting echocardiography (ECG) was performed by physicians if the diagnostic necessity arose. Patients with ECG signs of coronary artery ischemia were defined as ST-segment depression based on the Minnesota code.

RESULTS: Among 712 patients (36%) with GERD, ECG was performed in 171 (24%), and ischemic changes were detected in eight (5%). Four (50%) of these patients with abnormal findings upon ECG had no chest symptoms such as chest pain, chest oppression, or palpitations. These patients (0.6%; 4/712) were thought to have non-GERD heartburn, which may be related to ischemic heart disease. Of 281 patients who underwent ECG and did not have GERD symptoms, 20 (7%) had abnormal findings upon ECG. In patients with GERD symptoms and ECG signs of coronary artery ischemia, the prevalence of linked angina was considered to be 0.4% (8/1970 patients).

CONCLUSION: The present study suggested that ischemic heart disease might be found although a patient was referred to the hospital with a complaint of GERD symptoms. Physicians have to be concerned about missing clinically important coronary artery disease while evaluating patients for GERD symptoms.

Key words: Linked angina; Epidemiology; General practice; Electrocardiography; Gastroesophageal reflex disease

Peer reviewer: Tomohiko Shimatani, Assistant Professor, Department of General Medicine, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 7348551, Japan

Kato H, Ishii T, Akimoto T, Urita Y, Sugimoto M. Prevalence of linked angina and gastroesophageal reflux disease in general practice. *World J Gastroenterol* 2009; 15(14): 1764-1768 Available from: URL: http://www.wjgnet.com/1007-9327/15/1764.asp DOI: http://dx.doi.org/10.3748/wjg.15.1764

INTRODUCTION

Chest pain often precedes echocardiographic coronary angiography, electrocardiography (ECG), and scintigraphy for the diagnosis of angina. Many patients presenting to a hospital emergency room for chest pain turn out not to have coronary artery disease (CAD)[1]. According to data from a large university, 81%-86% of patients evaluated in an emergency room for acute chest pain did not have coronary ischemia[2,3]. It is well known that non-cardiac chest pain is closely related to gastroesophageal reflux diseases (GERD)[4,5]. Similarly, erosive esophagitis is not found in some patients with persistent GERD symptoms. Although GERD symptoms affect 10%-30% of the population in Western countries[6], endoscopic esophagitis is less prevalent, and is reported to occur in up to 2% of individuals[7-8]. Only one-third of GERD patients have endoscopic positive findings, while others have no obvious mucosal breaks, even though GERD symptoms are present[9]. Chest pain of esophageal origin can be difficult to distinguish from that caused

by cardiac ischemia because the distal esophagus and the heart share a common afferent vagal supply, and GERD can cause episodes of non-cardiac chest pain that resemble ischemic cardiac pain[10,11]. It is possible that GERD may be misclassified as angina pectoris and vice versa in clinical practice. The aim of this study was to evaluate the association between GERD and coronary heart disease and to clarify the presence of non-GERD heartburn.

MATERIALS AND METHODS

Ethics

The study was carried out in accordance with the Declaration of Helsinki, and approved by the ethical committee at Toho University.

Patients

Between October 2005 and May 2006, 1970 consecutive patients (934 men and 1036 women with a mean age of 43 years) who first attended the Outpatient Department of General Medicine and Emergency Care of Toho University Omori Hospital were enrolled. Informed consent was obtained from all the patients. None of the patients had a history of use of proton pump inhibitors, H2-receptor antagonists, antibiotics, steroids, or nonsteroidal anti-inflammatory drugs for a period of at least 2 mo before the investigation. Patients who had a previous history of partial gastrectomy were also excluded from the study.

Questionnaire

All of the patients who attended our hospital were asked to respond to the F-scale questionnaire regardless of their chief complaints. The questionnaire is a self-report instrument, written in a simple and easy-to-understand language, which contained 12 questions. As reported previously by Kusano *et al*[12], the following definitions were used to identify symptoms in the F-scale: (1) "Do you get heartburn?"; (2) "Is your stomach bloated?"; (3) "Does your stomach ever feel heavy after meals?"; (4) "Do you sometimes subconsciously rub your chest with your hand?"; (5) "Do you ever feel sick after meals?"; (6) "Do you get heartburn after meals?"; (7) "Do you have an unusual sensation in your throat?"; (8) "Do you feel full while eating meals?"; (9) "Do some things get stuck when you swallow?"; (10) "Do you get bitter liquid coming up into your throat?"; (11) "Do you belch a lot?"; and (12) "Do you get heartburn if you bend over?". Symptoms frequency was measured on the following scale: 0, never; 1, occasionally; 2, sometimes; 3, often; and 4, always. A score of more than 7 points, was considered positive for GERD.

Electrocardiogram

All patients had a careful history taken, and resting ECG was performed by physicians if diagnostic necessity arose. Patients with ECG signs of coronary artery ischemia were defined as having ST-segment depression based on the Minnesota code[13].

Table 1 Characteristics of study participants

Cardiogram	Abnormal	Normal	*P*
No. of patients	456	1514	
Age (yr)	48.2 ± 17.6 (16-91)	40.7 ± 15.7 (15-93)	< 0.001
Male/female	231/225	703/811	< 0.05
Hypertension	49/407	84/1430	< 0.001
Diabetes	36/420	45/1469	< 0.001
Hyperlipidemia	79/377	146/1473	< 0.001
Current smoker	156/300	488/1026	NS

Table 2 Relationship between GERD symptoms and ECG abmormalities

Cardiogram	Abnormal	Normal
GERD (+)	8	166
GERD (-)	20	261

Statistical analysis

All values are expressed as means ± SD. Comparisons of groups were made using Student's *t* test or chi-square tests as appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Overall, ECG was performed in 456 patients (23%, ECG group). The remaining 1514 patients were defined as controls. Patients in the ECG group were significantly older and the male to female ratio was significantly higher than in controls (Table 1). The prevalence of hypertension, diabetes mellitus, and hyperlipidemia was also significantly higher in the ECG group. There was no difference in the proportion of current smokers between the two groups.

Among 712 patients (36%) with GERD, ECG was performed in 171 patients (24%) and ischemic changes were detected in eight patients (5%). Four (50%) of these patients with abnormal findings upon ECG had no chest symptoms such as chest pain, chest oppression, or palpitations. These patients (0.6%; 4/712) were thought to have non-GERD heartburn, which may be related to ischemic heart disease. Of 281 patients who underwent ECG and did not have GERD symptoms, 20 (7%) had abnormal findings upon ECG (Table 2). No significant differences in the prevalence of ischemic changes were found between patients who underwent ECG and those who did not. As shown in Table 3, an exercise thallium test was performed in 12 GERD patients, of whom, one had ischemic coronary artery disease that was proven angiographically. In patients with GERD symptoms and ECG signs of coronary artery ischemia, the prevalence of linked angina, was considered to be 0.4% (8/1970 patients) (Figure 1). In contrast, patient with angina not related to GERD was found in 20 (1.0%).

DISCUSSION

Screening asymptomatic patients is an area of

Table 3 Number of patients undergoing additional cardiological tests

	GERD (+) n = 171 Abnormal findings		GERD (-) n = 285 Abnormal findings	
	(+)	(-)	(+)	(-)
ECG	8	163	20	265
Exercised thallium test	2	10	5	13
Cardioangiography	1	0	4	3

considerable interest because silent CAD is an important cause of premature death; many of these patients have three-vessel CAD or left main coronary artery stenosis[14]. Little is known, however, about the effects of intervention on asymptomatic disease, and screening strategies for asymptomatic CAD have been difficult to justify. Of patients with a low pre-test probability of CAD, only about 20% with a positive exercise test will have angiographically verified CAD[15]. Little evidence exists currently to support doing resting ECGs[16] or exercise tests[17] in patients without clinical evidence of CAD or cardiovascular risk factors.

When coronary arteries appear normal upon angiography, particularly when there is no other cardiac disorder or objective evidence of ischemia, a diagnosis of non-cardiac chest pain is made. In that particular study[18], cardiac mortality was 0.09% and coronary event rate was 0.65% per year, but 81% of patients had chest pain after 9 years follow-up. The clinician often is faced with the problem of a patient with comparatively mild coronary disease but persistent severe symptoms despite anti-anginal drugs. This subset of patients presents a difficult clinical problem because both the patient and physician usually perceive the pain to be of cardiac origin. It is probable that many of these patients have coexisting coronary disease and a symptomatic esophageal disorder. Symptoms of chest pain are a major source of concern for patients and physicians alike because they can sometimes be the harbinger of acute life-threatening events. However, many patients who describe chest pain that sounds identical to the type associated with significant cardiac disease can actually be free of such disease. After appropriate evaluations, about 40% of patients admitted for potential acute coronary syndromes turn out not to have CAD[19,20]. A study at the Emergency Room Assessment of Sestamibi for Evaluating Chest Pain Trial (ERASE trial), and a second study at a large hospital center in Philadelphia, showed that 81%-86% of all patients presenting to the emergency department with chest pain did not have a final diagnosis of cardiac ischemia[3,21]. Thus, differentiation between cardiac- and esophageal-origin chest pain is especially difficult since both organs have overlapping sensory pathways: Th1-Th4 for the heart and C8-TH10 for the esophagus. Moreover, they have autonomic nerve reflex, the so-called vagal visceral reflex function between the heart and organs of the gastrointestinal tract[22].

Direct mechanical effects between the esophagus

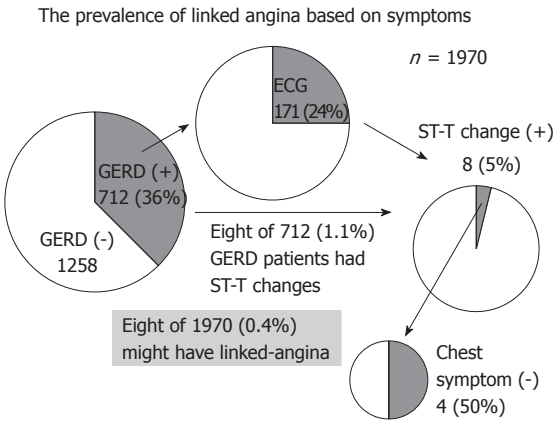

Figure 1 Prevalence of linked angina based on symptoms.

and the heart are thought to be compression of the left atrium by a huge hiatus hernia or extrinsic esophageal compression by cardiac enlargement. Other than these direct effects, a neural reflex, mediated by the vagus nerve, exists that allows changes in esophageal function to affect cardiac physiology[22]. Atrial tachycardia can be triggered by swallowing and belching, although the precise neural mechanism remains unclear[23]. Furthermore, bradycardia occurs in most people during balloon inflation within the esophagus and this may be blocked by atropine[24]. It has been suggested that esophageal dysfunction can itself trigger myocardial-ischemia-linked angina[25]. Smith *et al*[25] have coined the term "linked angina", which implies that gastrointestinal factors bring on attacks of genuine angina in patients with established CAD. They have explained this on the basis of cardiovascular changes, although gastoesophageal acid reflux may equally explain the phenomenon. Instillation of acid into the esophagus has been shown to significantly reduce the exertional angina threshold at which angina occurs or can provoke angina with ischemic ECG changes[26]. A previous animal study has demonstrated the reduced coronary flow caused by distension of the stomach that does not occur after vagal section or after the administration of atropine. This suggests that reflex coronary vasoconstriction is initiated by vagal irritation in the gastrointestinal tract[27]. Mellow *et al*[28] have demonstrated that acid perfusion of the esophagus results in reduced coronary blood flow in patients with proven CAD. It should be emphasized that 67% of patients felt chest pain and two-thirds of them developed ischemic ST-segment changes upon ECG. Dobrzycki *et al*[29] have also reported that GERD patients have a larger total ischemic burden and higher incidence of ST depression. Thus, spontaneous GER may have a role to play in the causation of or provocation of cardiac chest pain. Linked angina can be defined as that induced by GER. However, most patients with asymptomatic angina or symptoms, that do not reach the threshold required to define disease, do not refer to a hospital. Therefore, the present study was designed in the Department of General Medicine to evaluate the association between GERD and coronary heart disease in the general population because general

practice registers offer the best means of sampling the general population[30]. We hypothesized that the prevalence of CAD in GERD patients who were referred for the first time to the gastroenterology outpatient clinic because of heartburn may be substantial.

The present study revealed a small number of patients with abnormal ECG findings but without chest symptoms such as chest pain, chest oppression, or palpitations. This suggests that the extra-esophageal condition causes GERD symptoms and that angina may be misclassified as GERD. Such patients are often treated with proton pump inhibitors and chest pain disappears, which suggests that CAD may be overlooked. The results may therefore have clinical relevance, as it has been reported in a previous population-based, nested case-control study that patients with GERD have an increased risk of angina pectoris in the year after GERD diagnosis[31]. Actually, the incidence of reflux esophagitis is increasing as the population grows older, which makes it likely that such disease may be present in patients with CAD[32]. Physicians have to be concerned about missing clinically important CAD while evaluating patients for GERD symptoms.

COMMENTS

Background

Screening asymptomatic patients is an area of considerable interest because silent coronary artery disease (CAD) is an important cause of premature death, although many patients presenting to a hospital emergency room for chest pain turn out not to have CAD. It is well known that non-cardiac chest pain is closely related to gastroesophageal reflux diseases (GERD) and GERD symptoms affect 10%-30% of the population. Little is known, however, about the prevalence of linked angina, which is defined as angina induced by GER.

Research frontiers

In patients with GERD symptoms and echocardiography signs of coronary artery ischemia, prevalence of linked angina, was considered to be 0.4% (8/1970 patients). The prevalence may be increased when more sensitive tests such as angiography are used for diagnosis of angina.

Innovations and breakthroughs

Recent reports have highlighted the association between non-cardiac chest pain and GERD because both organs have overlapping sensory pathways. However, there have been few reports that GERD symptoms may be caused by ischemic heart disease. The present study is believed to be the first to evaluate the presence of non-GERD heartburn. GERD symptoms induced by coronary artery ischemia, so-called linked angina, certainly exist.

Applications

The study results suggest that an extra-esophageal condition causes GERD symptoms and that angina may be misclassified as GERD. Since patients with GERD have an increased risk of angina pectoris in the year after GERD diagnosis, physicians have to be concerned about missing clinically important CAD while evaluating patients for GERD symptoms.

Terminology

Linked angina is defined as angina induced by GER. GERD symptoms typically include heartburn and regurgitation. GERD is diagnosed according to symptoms regardless of the presence of endoscopically proven esophagitis.

Peer review

The authors examined the prevalence of linked angina. The results suggest the possibility that GERD patients also have coronary heart disease.

REFERENCES

1 **Kontos MC**. Evaluation of the Emergency Department chest pain patient. *Cardiol Rev* 2001; **9**: 266-275
2 **Udelson JE**, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, Heller GV, Hendel RC, Pope JH, Ruthazer R, Spiegler EJ, Woolard RH, Selker HP. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. *JAMA* 2002; **288**: 2693-2700
3 **Katz PO**, Castell DO. Approach to the patient with unexplained chest pain. *Am J Gastroenterol* 2000; **95**: S4-S8
4 **Shrestha S**, Pasricha PJ. Update on noncardiac chest pain. *Dig Dis* 2000; **18**: 138-146
5 **Chahal PS**, Rao SS. Functional chest pain: nociception and visceral hyperalgesia. *J Clin Gastroenterol* 2005; **39**: S204-S209; discussion S210
6 **Holtmann G**. Reflux disease: the disorder of the third millennium. *Eur J Gastroenterol Hepatol* 2001; **13** Suppl 1: S5-S11
7 **Mansi C**, Savarino V, Mela GS, Picciotto A, Mele MR, Celle G. Are clinical patterns of dyspepsia a valid guideline for appropriate use of endoscopy? A report on 2253 dyspeptic patients. *Am J Gastroenterol* 1993; **88**: 1011-1015
8 **Kagevi I**, Löfstedt S, Persson LG. Endoscopic findings and diagnoses in unselected dyspeptic patients at a primary health care center. *Scand J Gastroenterol* 1989; **24**: 145-150
9 **Dent J**. Gastroesophageal reflux disease. *Digestion* 1998; **59**: 433-445
10 **Liuzzo JP**, Ambrose JA. Chest pain from gastroesophageal reflux disease in patients with coronary artery disease. *Cardiol Rev* 2005; **13**: 167-173
11 **Johansson S**, Wallander MA, Ruigómez A, García Rodríguez LA. Is there any association between myocardial infarction, gastro-oesophageal reflux disease and acid-suppressing drugs? *Aliment Pharmacol Ther* 2003; **18**: 973-978
12 **Kusano M**, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, Kuribayashi S, Higuchi T, Zai H, Ino K, Horikoshi T, Sugiyama T, Toki M, Ohwada T, Mori M. Development and evaluation of FSSG: frequency scale for the symptoms of GERD. *J Gastroenterol* 2004; **39**: 888-891
13 **Macfarlane PW**, Latif S. Automated serial ECG comparison based on the Minnesota code. *J Electrocardiol* 1996; **29** Suppl: 29-34
14 **Gordon T**, Kannel WB. Premature mortality from coronary heart disease. The Framingham study. *JAMA* 1971; **215**: 1617-1625
15 **Detrano R**, Froelicher V. A logical approach to screening for coronary artery disease. *Ann Intern Med* 1987; **106**: 846-852
16 **Sox HC Jr**, Garber AM, Littenberg B. The resting electrocardiogram as a screening test. A clinical analysis. *Ann Intern Med* 1989; **111**: 489-502
17 **Sox HC Jr**, Littenberg B, Garber AM. The role of exercise testing in screening for coronary artery disease. *Ann Intern Med* 1989; **110**: 456-469
18 **Lichtlen PR**, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol* 1995; **25**: 1013-1018
19 **Pope JH**, Ruthazer R, Beshansky JR, Griffith JL, Selker HP. Clinical Features of Emergency Department Patients Presenting with Symptoms Suggestive of Acute Cardiac Ischemia: A Multicenter Study. *J Thromb Thrombolysis* 1998; **6**: 63-74
20 **Diop D**, Aghababian RV. Definition, classification, and pathophysiology of acute coronary ischemic syndromes. *Emerg Med Clin North Am* 2001; **19**: 259-267
21 **Liuzzo JP**, Ambrose JA, Diggs P. Proton-pump inhibitor use by coronary artery disease patients is associated with fewer chest pain episodes, emergency department visits and hospitalizations. *Aliment Pharmacol Ther* 2005; **22**: 95-100
22 **Cunningham ET Jr**, Ravich WJ, Jones B, Donner MW. Vagal reflexes referred from the upper aerodigestive tract: an infrequently recognized cause of common cardiorespiratory responses. *Ann Intern Med* 1992; **116**: 575-582
23 **Wilmshurst PT**. Tachyarrhythmias triggered by swallowing and belching. *Heart* 1999; **81**: 313-315

24 **Kakuchi H**, Sato N, Kawamura Y. Swallow syncope associated with complete atrioventricular block and vasovagal syncope. *Heart* 2000; **83**: 702-704
25 **Smith KS**, Papp C. Episodic, postural, and linked angina. *Br Med J* 1962; **2**: 1425-1430
26 **Davies HA**, Page Z, Rush EM, Brown AL, Lewis MJ, Petch MC. Oesophageal stimulation lowers exertional angina threshold. *Lancet* 1985; **1**: 1011-1014
27 **Chauhan A**, Petch MC, Schofield PM. Cardio-oesophageal reflex in humans as a mechanism for "linked angina'. *Eur Heart J* 1996; **17**: 407-413
28 **Mellow MH**, Simpson AG, Watt L, Schoolmeester L, Haye OL. Esophageal acid perfusion in coronary artery disease. Induction of myocardial ischemia. *Gastroenterology* 1983; **85**: 306-312
29 **Dobrzycki S**, Baniukiewicz A, Korecki J, Bachórzewska-Gajewska H, Prokopczuk P, Musial WJ, Kamiński KA, Dabrowski A. Does gastro-esophageal reflux provoke the myocardial ischemia in patients with CAD? *Int J Cardiol* 2005; **104**: 67-72
30 **Fleming DM**. Morbidity registration and the fourth general practice morbidity survey in England and Wales. *Scand J Prim Health Care Suppl* 1993; **2**: 37-41
31 **Ruigómez A**, García Rodríguez LA, Wallander MA, Johansson S, Graffner H, Dent J. Natural history of gastro-oesophageal reflux disease diagnosed in general practice. *Aliment Pharmacol Ther* 2004; **20**: 751-760
32 **Svensson O**, Stenport G, Tibbling L, Wranne B. Oesophageal function and coronary angiogram in patients with disabling chest pain. *Acta Med Scand* 1978; **204**: 173-178

S- Editor Li LF **L- Editor** Kerr C **E- Editor** Zheng XM