

## Prevalence of Gastrointestinal Diseases and Treatment Status in Noncardiac Chest Pain Patients

Sung-Hun Park, MD, Ja Yeon Choi, MD, Eun Jin Park, MD, Jae Joong Lee, MD, Sunki Lee, MD, Jin Oh Na, MD, Cheol Ung Choi, MD, Hong Euy Lim, MD, Jin Won Kim, MD, Eung Ju Kim, MD, Seung-Woon Rha, MD, Hong Seog Seo, MD, Dong Joo Oh, MD, and Chang Gyu Park, MD

Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea

**Background and Objectives:** We evaluated the prevalence of gastroesophageal reflux diseases (GERD) in noncardiac chest pain (NCCP) patients, risk factors for GERD, and status of prescriptions for GERD in Korean population.

**Subjects and Methods:** This was a retrospective non-interventional observational nation-wide 45-center study. Patients with a normal coronary angiogram (CAG) and upper gastroendoscopy within 2 years after CAG were enrolled. The prevalence of GERD was examined. Other gastrointestinal diseases including peptic ulcer diseases or gastritis were also examined. Risk factors for GERD were compared between the GERD group and non-GERD group. The ratio of patients medicated for gastrointestinal diseases (antacids or proton-pump inhibitor) was also examined.

**Results:** Nine hundred four patients were enrolled. Among the NCCP patients, GERD was present in 436 (48.2%), peptic ulcer disease in 154 patients (17.0%), and gastritis in 659 (72.9%). There was no difference in risk factors for GERD between the GERD and non-GERD patients. Medications for GERD and other gastrointestinal diseases were prescribed in 742 (82.1%) patients.

**Conclusion:** GERD was common (42.8%) in Korean NCCP patients and most (82.1%) received the prescription of gastrointestinal medications. No differences were evident in risk factors between GERD and non-GERD patients. (**Korean Circ J 2015;45(6):469-472**)

**KEY WORDS:** Chest pain; Gastroesophageal reflux.

### Introduction

Noncardiac chest pain (NCCP) is defined as recurrent retrosternal angina-like pain in patients with normal cardiac evaluations. The prevalence of NCCP in western countries was reported as 25% to 35% in one population-based-study.<sup>1)</sup>

Physicians perform cardiac work-up first when evaluating

patients with chest pain in clinical practice, because differential diagnosis of chest pain is not easy and misdiagnosis of coronary artery disease can be life-threatening. After ruling out cardiac chest pain by an exercise electrocardiogram (EKG), echocardiography and coronary angiogram (CAG), we refer patients to the gastroenterology department for further work-up including upper gastroendoscopy because gastroesophageal reflux disease (GERD) is by far the most common cause of NCCP.<sup>2)</sup> This is the typical scenario for NCCP cases in clinical practice.<sup>3)</sup>

In non-GERD-related NCCP, esophageal dysmotility and esophageal hypersensitivity have been suggested as main causes.<sup>4)</sup> Besides those originated from the esophagus, various causes of NCCP include microvascular angina, musculoskeletal disorders, psychological disorders, mediastinal and pleural diseases, and biliary and gastrointestinal diseases.<sup>5)</sup>

Patients with NCCP can experience a poor quality of life and become frequent users of health-care resources. This can be an economic burden with respect to medical costs.<sup>6)</sup> Therefore, better knowledge of NCCP in the general population is necessary. However,

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**Correspondence:** Chang Gyu Park, MD, Cardiovascular Center, Korea University Guro Hospital, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea  
Tel: 82-2-2626-3019, Fax: 82-2-864-3062  
Email: parkcg@kumc.or.kr

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little information is available, aside from an examination of NCCP among patients confirmed by CAG and vasospasm examinations.<sup>7)</sup>

The aim of this study was to examine the prevalence of GERD and other esophageal or gastric diseases among NCCP patients. Risk factors of GERD, such as alcohol consumption, smoking, obesity, and the rate of medical prescriptions for GERD or gastrointestinal diseases, were also examined.

## Subjects and Methods

This was a retrospective non-interventional observational multicenter study performed by reviewing the medical records including gastroendoscopy reports. The study was conducted according to the provisions of the Declaration of Helsinki, and all patients were informed about the study. Written consent documents were confirmed for each patient.

A total of 904 Korean patients were enrolled in from outpatient clinics in 45 hospitals nationwide in Korea from January 2010 to January 2011. Inclusion criteria were age over 20 years, chest pain but normal or below 50% coronary artery stenosis by CAG, and history of upper gastroendoscopy within 2 years after CAG. Patients were excluded if they had a coronary vasospasm, severe hypertension (systolic blood pressure  $\geq$  180 mmHg, diastolic blood pressure  $\geq$  110 mmHg whether or not on medications), cardiomyopathy, congestive heart failure, atrial fibrillation (AF), or other severe arrhythmia (any tachyarrhythmia or bradyarrhythmia with hemodynamic significance or related symptom).

The provocation test was performed by administration of acetylcholine or ergonovine. Acetylcholine was injected via the intracoronary route with incremental doses of 20, 50, and 100  $\mu$ g over a 1-minute period, with at least 5 minutes between injections. Ergonovine was injected via the same route at a rate of 10  $\mu$ g/minute for 4 minutes to a total dose of 40  $\mu$ g in the right coronary artery, and 16  $\mu$ g/minute for 4 minutes to a total dose of 64  $\mu$ g in the left coronary artery with an interval of at least 5 minutes between injections. During the test, electrocardiography (ECG) (lead II) and blood pressure were monitored continuously. It was reported as positive if quantitative coronary angiogram after acetylcholine or ergonovine resulted in over 70% luminal narrowing after provocation or ischemic ECG changes, such as ST-T segment elevation, depression ( $\geq$  1mm) or T wave inversion, or angina/chest pain. The provocation study protocol is almost identical between the physicians, with the exception of dosage.

In general, GERD could be diagnosed on the basis of typical symptoms, for example heartburn, regurgitation, and dysphagia. When only an atypical symptom existed, GERD could be diagnosed with gastroendoscopy, esophagography, 24-hour esophageal pH-

metry, esophageal manometry, and Bernst provocation test by demonstrating reflux. In this study, GERD was diagnosed if there was any mucosal break with Los Angeles classification A to D in endoscopic findings.

Primary endpoint was the prevalence of GERD among NCCP patients. Secondary endpoints were the prevalence of risk factors including alcohol consumption, smoking, and obesity. Prevalence of other upper gastrointestinal diseases except GERD in NCCP patients and the status of prescriptions for gastrointestinal medications were also examined.

Statistical analyses were performed with SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). The analyses included Student's t-test and chi-squared test. A  $p \leq 0.05$  was considered to be statistically significant.

## Results

A total of 904 consecutive patients with NCCP (518 females, 57.3%; 386 males, 42.7%) were enrolled. The demographic data is provided in Table 1. The mean age of patients was  $63.05 \pm 11.7$  years.

The prevalence of GERD and other upper gastrointestinal diseases are summarized in Table 2. GERD were present in 436 (48.2%) patients, peptic ulcer disease in 154 (17.0%) patients, and gastritis in 659 (72.9%) patients.

Risk factors for GERD in the GERD and non-GERD groups are presented in Table 3. Obesity, smoking, and diabetes are established risk factors for GERD. But, presently there were no significant differences in risk factors between the groups. Further analyses involving division of patients into seven groups – GERD only, peptic ulcer only, gastritis only, GERD and peptic ulcer, GERD and gastritis,

**Table 1.** Baseline patient characteristics

|                                      |                      |
|--------------------------------------|----------------------|
| Mean age, years                      | 63.05 $\pm$ 11.7     |
| Sex, male/female (%)                 | 384 (42.7)/518(57.3) |
| Body mass index (kg/m <sup>2</sup> ) | 24.91 $\pm$ 3.26     |
| Alcohol (%)                          | 146 (16.2)           |
| Smoking (%)                          | 174 (19.2)           |
| Hypertension (%)                     | 485 (53.7)           |
| Diabetes mellitus (%)                | 157 (17.4)           |
| Hyperlipidemia (%)                   | 205 (22.7)           |

Data are n (%) or mean $\pm$ standard deviation

**Table 2.** Prevalence of GERD and other gastrointestinal diseases

|                           |            |
|---------------------------|------------|
| GERD (%)                  | 436 (48.2) |
| Peptic ulcer diseases (%) | 154 (17.0) |
| Gastritis (%)             | 659 (72.9) |

Data are expressed as n (%). GERD: gastroesophageal reflux diseases

**Table 3.** Risk factors for GERD between the groups

|                                      | GERD        | non-GERD    | p     |
|--------------------------------------|-------------|-------------|-------|
| Mean age (years)                     | 62.53±11.57 | 63.54±11.80 | 0.196 |
| Male (%)                             | 190 (49.2)  | 196 (41.9)  | 0.327 |
| Body mass index (kg/m <sup>2</sup> ) | 25.10±3.22  | 24.74±3.30  | 0.113 |
| Alcohol (%)                          | 71 (16.3)   | 75 (16.0)   | 0.396 |
| Smoking (%)                          | 82 (18.8)   | 92 (19.7)   | 0.378 |
| Hypertension (%)                     | 241 (55.3)  | 244 (52.1)  | 0.190 |
| Diabetes mellitus (%)                | 69 (15.8)   | 88 (18.8)   | 0.137 |
| Hyperlipidemia (%)                   | 97 (22.2)   | 108 (23.1)  | 0.414 |
| Aspirin (%)                          | 176 (40.4)  | 193 (41.2)  | 0.421 |
| NSAIDs (%)                           | 7 (1.6)     | 6 (1.3)     | 0.448 |
| Anticoagulation (%)                  | 42 (9.6)    | 40 (8.5)    | 0.325 |
| GI medication (%)                    | 357 (81.9)  | 385 (82.3)  | 0.474 |

Values are expressed as mean±standard deviation for quantitative variables or n (%) for qualitative variables. GERD: gastroesophageal reflux diseases, NSAID: non-steroidal antiinflammatory drug, GI: gastrointestinal

peptic ulcer and gastritis, GERD and peptic ulcer and gastritis – also demonstrated no significant difference in risk factors, except that alcoholics were more common in the last group {14/52 (26.9%) in the GERD and peptic ulcer and gastritis group versus 135/855 (15.7%) of the no gastrointestinal disease group}.

Medications for GERD and other gastrointestinal diseases were prescribed in 742 (82.1%) of the NCCP patients. There was no significant differences in medications between GERD and non-GERD groups (357, 81.9% versus 385, 82.3%; p=0.474).

## Discussion

Recently, the Montreal workshop report defined GERD as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications.<sup>3)</sup> The prevalence of GERD in Korea range from 3% to 16%, and is expected to increase as the society becomes increasingly westernized.<sup>8)</sup>

The population prevalence of NCCP ranges up to 25%.<sup>9)</sup> NCCP is indistinguishable from cardiac chest pain. So after thorough cardiac evaluation, we usually prescribe gastrointestinal medications including proton-pump-inhibitors (PPIs) or refer the patients to the gastrointestinal department for further work-up including upper gastroendoscopy. But, NCCP patients frequently utilize healthcare resources resulting in negative impact on patient's quality of life and social wellbeing as well as an economic burden.<sup>10)</sup>

One-fifth of GERD patients can experience chest pain.<sup>11)</sup> Appreciable numbers of patients with reflux esophagitis or non-erosive reflux disorder (NERD) can experience chest pain (16.5% and 33.0%, respectively).<sup>8)</sup> Choi et al.<sup>7)</sup> reported that 25.5% of NCCP was

related with GERD. These studies were single center studies and are not representative of the entire Korean population.

In this study, GERD was present in 436 (48.2%) of the NCCP patients. Peptic ulcer diseases including gastric ulcers and duodenal ulcers were present in 154 (17.0%) of the 904 NCCP patients. The prevalence rate of GERD among NCCP patients in this study was similar with previous studies including East Asia (Hong Kong).<sup>2)12)</sup> Another study<sup>11)</sup> reported a prevalence rate of GERD in the general population ranged from 3% to 16%. GERD would appear to be more common in NCCP patients than in the general population.

NCCP is reportedly significantly more common in middle-aged women compared with men.<sup>7)</sup> The higher incidence in women has been explained as their greater predilection for anxiety and depression.<sup>13)</sup> Presently, 518 (57.3%) of 904 NCCP patients were women, with no statistically significant difference in risk factors between the GERD group and non-GERD group. Gastrointestinal medications were prescribed in 742 (82.1%) of the NCCP patients. This could reflect the greater tendency of physicians to prescribe gastrointestinal medications to NCCP patients under the assumption that NCCP is caused by gastrointestinal diseases including GERD or peptic ulcer.

The importance of gastroesophageal reflux in causing NCCP has also been demonstrated by analysis of treatment trials of acid suppression in NCCP. A recent meta-analysis reported improved symptoms by PPIs in 50% to 75% of NCCP patients.<sup>14)</sup>

This study is significant in that all the subjects were confirmed to have NCCP by coronary angiogram and vasospasm examinations. Previous studies<sup>12)7)</sup> defined NCCP with only symptom questionnaire and/or exercise EKG, or, for subjects with CAG, did not include a provocation study to rule out vasospasm angina. Most of the

previous studies were single-center studies. The present study was a nation-wide, multicenter study involving 45 hospitals. It is more representative of the general Korean population.<sup>7,15)</sup>

There are some limitations in this study. First, this was mostly retrospective. To conclude that GERD is the most common cause of NCCP will require a prospective study. Second, we hypothesized that NCCP was caused by GERD if NCCP patients had a GERD on the basis of an upper gastroendoscopy. However, GERD could be a bystander, with NCCP caused by other etiologies. Third, the Montreal workshop classified GERD as reflux esophagitis and NERD by upper endoscopic findings. NERD could not be diagnosed by upper gastroendoscopy alone and required a 24-hour esophageal pH-metry and symptom questionnaire.<sup>3)</sup> However, we considered only reflux esophagitis as GERD. Therefore, it is possible that patients with NERD were excluded. Fourth, no detailed information was available on chest pain, for example duration or characters, gastrointestinal medications, and exact structural heart disease status by echocardiography. Fifth, if there were no abnormal findings in gastroendoscopy, no further evaluations were carried out for other gastrointestinal diseases like esophageal motility disorder or pancreatobiliary disease.

In conclusion, GERD is significantly common in Korean NCCP patients and most were prescribed gastrointestinal medications. No differences in risk factors between GERD and non-GERD patients were evident. Further prospective information is needed, especially concerning NCCP not responding to gastrointestinal medications.

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