Acid Reflux in Patients with Coronary Artery Disease and Refractory Chest Pain

Yijun Liu, Suyu He, Yongjun Chen, Jianyu Xu, Chuansu Tang, Yi Tang and Guiquan Luo

Abstract

Objective  To investigate the influence of acid reflux on chest pain and ischemic events and the effects of cardiac drugs on acid reflux in patients with coronary artery disease (CAD) and refractory chest pain.

Methods  Simultaneous 24-hour esophageal pH monitoring and 24-hour continuous electrocardiogram (ECG) (Holter) results were obtained for 64 patients. Ischemic events and cardiac drug prescriptions were compared between the patients with and without gastroesophageal reflux disease (GERD). Patients fulfilling the GERD criteria received 14-day therapy with omeprazole at a dose of 20 mg bid. The results of the 24-hour pH monitoring, Holter and the SF-36 questionnaire were compared before treatment and again after two weeks of therapy.

Results  GERD was identified in 38 (69%) patients, with 49% of all chest pain occurring in association with acid reflux. A higher incidence (p=0.033) and longer duration (p=0.040) of ischemic events were observed in the GERD (+) patients. More frequent combined use of cardiac drugs was found in the GERD (+) patients. However, fewer ischemic events and greater total SF-36 survey scores were noted after PPI therapy in the GERD (+) patients.

Conclusion  Acid reflux is common in patients with CAD and refractory chest pain. Refractory chest pain in patients with CAD can be partially noncardiac chest pain (NCCP) secondary to acid reflux. The combined use of common cardiac drugs may predispose or aggravate GERD. Short-term proton pump inhibitor (PPI) therapy not only restores a normal esophageal pH, but also significantly improves the general health-related quality of life (HRQL) of patients.

Key words: refractory chest pain, coronary artery disease, gastroesophageal reflux disease, 24-h ECG monitoring, 24-h esophageal pH monitoring

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Introduction

A large number of patients with coronary artery disease (CAD) have chest pain that is unresponsive to both conventional medical therapy and revascularization techniques (1). This subset of CAD patients is considered to have refractory chest pain, which constitutes an important and common clinical problem that induces anxiety in both patients and physicians. It also presents a difficult clinical problem because both the patient and the physician usually perceive the pain to be of cardiac origin, when in fact, the chest pain experienced by patients with CAD can be partially of noncardiac origin.

Making a differential diagnosis of chest pain is often difficult. Evaluating the symptoms themselves is not sufficient to predict the underlying disease. Because the distal esophagus and heart share a common afferent vagal supply, mechanical and/or chemical stimulation of the esophagus can evoke myocardial ischemia, leading to chest pain (2-5). In fact, noncardiac chest pain (NCCP) gastroesophageal reflux occurs at the same frequency in patients with normal and pathological coronary angiographies. Many physicians overlook this diagnostic possibility, especially when they are

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aware that the patient has CAD, which leads them to search aggressively for the original cardiac problem. As a matter of fact, among patients with CAD experiencing chest pain, 50% have gastroesophageal reflux disease (GERD) (6). Furthermore, the most common cardiac drugs used to treat CAD, particularly nitrates, calcium-channel blockers (CCBs) and antplatelet drugs, may either predispose CAD patients to GERD or aggravate preexisting GERD (7-9); hence, escalating treatment can increase chest pain, leading the physician to the erroneous conclusion that the CAD is worsening. Previous studies have provided support for the use of acid suppression with proton pump inhibitors in patients with CAD to decrease pain symptoms and improve the general health-related quality of life (HRQL) (10, 11). However, most of these studies were conducted in CAD patients with common chest pain, not refractory chest pain. Furthermore, empirical acid suppression is often prescribed in such studies. No studies have been performed to investigate refractory chest pain in patients with CAD who have remained symptomatic despite receiving optimal antianginal therapy. In fact, acid suppression therapy may be particularly efficacious for those patients with known GERD-related NCCP.

Therefore, the purpose of this study was to test the hypothesis that refractory chest pain in patients with CAD may thus be partially due to NCCP secondary to acid reflux. We also investigated the possible effects of common cardiac drugs, used alone or in combination, on GERD and the efficacy of acid suppression with the addition of a proton pump inhibitor (PPI) (omeprazole) to cardiac medical therapy in patients with known GERD-related NCCP.

Materials and Methods

Patients

Between January 2006 and December 2011, approximately 3,200 patients were referred for angiography by the three cardiologists who participated in this study. Of these patients, 2,040 were angiographically proven to have CAD. We selected 64 patients from the 2,040 patients with refractory chest pain that could not be relieved by aggressive medical and/or surgical therapy and enrolled them in this investigation. The inclusion criteria were as follows: 1) chest pain lasting for at least two months prior to the study; 2) chest pain that could not be relieved by aggressive medical and/or surgical therapy; 3) a frequency of chest pain episodes of no fewer than three times per week; 4) at least 50% narrowing of the coronary vessels on angiography that was unsuitable for revascularization, as declared by at least two interventional cardiologists; 5) 40-70 years of age; and Canadian Cardiovascular Society (CCS) functional classes II-III. The exclusion criteria were as follows: 6) contraindications for performing any test used in the study; 7) upper gastrointestinal disorders that were clearly identified on prior investigations (peptic ulcers, etc.) or typical symptoms (heartburn occurring more than once every two weeks); 8) the use of acid-suppression therapy prior to the study (patients receiving empirical acid-suppression were allowed if the treatment been stopped for at least four weeks); and 9) patients who declined to participate in the study. Patients who were found to have abnormal upper gastrointestinal endoscopy findings for reasons other than reflux disease or abnormal esophageal manometry findings were also excluded from the study.

Methods

Sixty-four patients fulfilled the inclusion and exclusion criteria and were informed of the purpose and principles of the study. All patients underwent upper gastrointestinal endoscopy. Then, simultaneous 24-hour ambulatory esophageal pH and electrocardiogram (ECG) monitoring were performed. First, esophageal manometry was used to localize the upper margin of the lower esophageal sphincter (LES) for subsequent placement of the pH catheter. Esophageal manometry was performed using a multi-channel water-perfused manometry catheter (Medical Measurement Systems, B.V., An Enschede, Netherlands). The catheter was inserted into the esophagus via the nasal passage to determine the position of the LES. The manometry catheter was then withdrawn. Immediately after esophageal manometry, simultaneous 24-hour esophageal pH and Holter monitoring were performed. A single-channel pH electrode (Medical Measurement Systems. B.V., An Enschede, Netherlands) was inserted nasally and positioned 5 cm above the upper margin of the LES. The reference electrode was placed on the anterior chest. Prior calibration of the electrode and recorder was performed in standard buffer solutions at pH 7 and pH 4 at 20°C. The electrode was connected to a tape recorder that was carried by the patient on his/her hip during the duration of the study. The patients were then connected to an ambulatory Holter monitor recorder (BI9800, Biomedical Instrument, Shenzhen, China). The leads were placed to obtain recordings comparable to those from the leads and V, on standard 12-lead electrocardiography. The data were collected on a cassette tape. The 24-hour esophageal pH and Holter were synchronized to start simultaneously by depressing the start button on the two recorders together. The patients were asked to record the start and completion of the test on a diary card. The patients were also instructed to keep records of their meal times, smoking, time of assuming a supine posture for sleep and time of arising in the morning. Pain events or other symptoms were entered into the pH recorder by depressing the event marker once at the start of each pain or other symptom episode. The patients were asked to continue their usual activities and cardiac medications. Sparkling water and sour meals were prohibited during the study period. The patients were asked to return after a 24-hour period to have both recorders turned off simultaneously and removed. All recorded data were analyzed.

The esophageal pH data were analyzed using an esophageal analysis program (gastrosoft, Synectics, Stockholm, Sweden). The percentage of time with an esophageal pH <4
Table 1. Clinical and Angiographic Characteristic of Patients

<table>
<thead>
<tr>
<th>Study population</th>
<th>GERD (+) 38 patients N (%)</th>
<th>GERD (-) 17 patients N (%)</th>
<th>all 55 patients N (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>58.2±8.7</td>
<td>60.6±8.4</td>
<td>59.0±8.6</td>
<td>0.371</td>
</tr>
<tr>
<td>Males</td>
<td>32 (84)</td>
<td>15 (88)</td>
<td>47 (85)</td>
<td>0.597</td>
</tr>
<tr>
<td>HBP</td>
<td>24 (63)</td>
<td>12 (71)</td>
<td>36 (65)</td>
<td>0.596</td>
</tr>
<tr>
<td>DM</td>
<td>8 (21)</td>
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<td>Class II CCS</td>
<td>17 (45)</td>
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<td>1 VD</td>
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Results expressed as x±SD. HBP: high blood pressure, MI: myocardial infarction, VD: vessel disease.

was calculated, and pathological esophageal acid reflux (PEAR) was determined to be present when the esophageal pH was below 4 for ≥4.0% of the test period (12). The symptom index (SI) was calculated for each chest pain incident in relation to the acid reflux episodes. Chest pain was considered to be associated with reflux if it was preceded by a reflux episode within two minutes (13). A positive SI was defined as >50% of the symptoms being associated with pathological reflux (14). The presence of PEAR and/or a positive SI was considered to be evidence suggestive of a GERD diagnosis (12, 15).

The ambulatory ECG data were analyzed by the Holter system. Ischemic ECG changes were defined as a 1-mm horizontal depression or down-sloping for 80 ms from the J-point. ST-segment depression provoked by gastroesophageal reflux was defined as ST-segment depression occurring during and up to 10 minutes after an acid reflux episode (16). The number and total time of ST-segment depression episodes were measured as indicators of the ischemic burden.

**Therapy**

Thirty-eight patients (27 of whom completed the study) fulfilling the GERD criteria received 14-day therapy with omeprazole at a dose of 20 mg bid in an open-label study. On the 14th day of therapy, simultaneous Holter and esophageal pH monitoring was repeated. At the same time, the patients’ quality of life was assessed using the SF-36 Health Survey, which is the most commonly used generic HRQL test. Before the start of the trial and at the end of the second week, the patients completed the SF-36 quality of life questionnaire. The original answers obtained for the questions on the SF-36 questionnaire were re-coded and scored using the original 0-100 scoring algorithms then averaged using their respective scale and forms as per the instructions. Three summarized measures were calculated as follows: the total average SF-36 survey score, the physical health component and the mental health component. The first was the sum of all eight health concept scores, the second, known as the physical health component, was the sum of the physical components, and the third arose from summarizing the energy/fatigue (vitality), social functioning, role limitations due to emotional problems and mental health scale scores.

**Ethics**

All subjects gave their informed consent. The study protocol was approved by the Suining Central Hospital’s committee on human research.

**Statistical analysis**

The statistical analysis was performed using the SPSS software package (SPSS statistics base 17.0). Nonparametric statistical tests were used because the monitoring data were not normally distributed. The results were expressed as the mean and range. Intergroup differences were analyzed using the Mann-Whitney U nonparametric test. The Wilcoxon matched-pairs signed-ranks test was used to compare the ECG and esophageal pH monitoring variables before and after therapy with omeprazole. A difference was considered to be statistically significant when the p value was <0.05.

**Results**

There were no differences between the groups regarding the mean age, the rate of hypertension, the presence of diabetes mellitus, a past history of myocardial infarction or the severity of angina as classified according to the CCS. The severity and localization of coronary lesions and the rate of antiangiinal drug administration (β-blockers, nitrates, antiplatelets, CCB) were also comparable between the groups (Tables 1, 3).

**Results of pH and Holter monitoring**

During the study, there was a total of 1,136 acid reflux episodes in 55 patients. GERD was identified in 38 (69%) patients with a mean esophageal pH of 14.8% (range 2.0-31.0) and 32 (58%) patients had PEAR with a mean esophageal pH of 17.0% (range 4.2-31.0). Six (11%) patients had SI (+) with a mean esophageal pH of 3.0% (range 2.0-3.9) and 13 (24%) patients had both with a mean pH of 10.1% (range 2.0-31.0). ST segment depression indicative of cardiac ischemia was observed on a total of 231 occasions, and a median of six ST segment shifts was seen (range 1-30). Among the 231 episodes, 74 (32%) were time-dependent on

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Table 2. Comparison of Number of ST Depression, Total Ischemic Time and Pain Episodes in Patients with GERD (+) or Not

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<th>Parameter</th>
<th>GERD(+)</th>
<th>GERD(-)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ST depression episode</td>
<td>6.1(1-24)</td>
<td>4.1(1-15)</td>
<td>0.033</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>87.7(19-178)</td>
<td>63.7(16-157)</td>
<td>0.040</td>
</tr>
<tr>
<td>Pain associated with ischemia</td>
<td>1.1(0-4)</td>
<td>2(0-5)</td>
<td>0.091</td>
</tr>
<tr>
<td>Pain episodes</td>
<td>3.5(1-11)</td>
<td>3.0(1-8)</td>
<td>0.045</td>
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Results expressed as median (range). No. of ST depression: the number of ST-segment depression episodes; Total ischemic time: the total time of ST-segment depression episodes.
The chest pain experienced by patients with CAD can be of noncardiac origin, and the symptoms are frequently related to gastroesophageal reflux. Patients with known CAD comprise a challenging group to manage if concomitant NCCP is present. The patient’s prior history sets a precedent for future clinical evaluation and management. In one study, chest pain evaluated by cardiologists was clinically misdiagnosed as cardiac disease in 25% of patients (17). A number of previous studies have provided evidence that the reflux prevalence is over 40% in patients with CAD, with 40-70% of cases of reflux being directly associated with chest pain symptoms (18-23). However, this study is the first to investigate acid reflux in patients with CAD and refractory chest pain. In this study, we attempted to answer three questions: Is the chest pain and ischemic condition related to GERD? Does cardiac drug prescription predispose or aggravate acid reflux. A manual method of performing an exact time analysis of acid reflux episodes and ST-segment depression episodes on ECG was used to assess the possible correlation. A significantly higher incidence (p=0.033) and longer duration of ischemic events (p=0.040) were observed in the patients with GERD (+). There were no differences between the GERD (+) and GERD (-) groups in terms of pain episodes associated with ST-segment depression episodes on ECG (p=0.091) (see Table 2).

**Pain and its association with acid reflux**

A total of 245 pain episodes were recorded (median 4.5 per patient, range 1-11) in 55 patients. Compared with the GERD (-) group, more pain episodes were observed in the patients with GERD (+) (median 3.5 per patient, range 1-11). One hundred and twenty (49%) of the 245 pain episodes occurred in association with acid reflux, and 37 pain episodes (15%) coincided with both acid reflux and ST-segment shifts (see Table 2).

**Cardiac drug prescriptions and GERD**

Compared with the GERD (-) group, the combined use of common cardiac drugs, especially the combination of CCB, antiplatelets and nitrates (p=0.014) and the combination of CCB, antiplatelets, β-blockers and nitrates (p=0.034), was more frequent in the GERD (+) group (see Table 3).

**24-hour pH and Holter monitoring, SF-36 survey for therapy results**

Thirty-eight patients with GERD (+) entered the treatment trial. However, only 27 patients completed the two-week trial (Figure). The acid-suppression therapy reduced all analyzed parameters of esophageal pH monitoring, the number of ST depressions, the total ischemic time and the total number of pain episodes (Table 4). However, there were no significant differences before and after therapy in the number of pain episodes associated with ST-segment depression (p=0.058). In comparison to the values obtained before the two-week trial period, patients who accepted the two-week acid-suppression therapy had significantly greater total SF-36 survey scores (the sum of all eight of the health concepts), average values for bodily pain, general health perception scales and physical health scores summarized into components (Table 5).

When the results of the 24-hour pH and continuous Holter monitoring were compared, no significant differences were noted in the localization or extensiveness of the coronary lesions.

**Discussion**

The chest pain experienced by patients with CAD can be of noncardiac origin, and the symptoms are frequently related to gastroesophageal reflux. Patients with known CAD comprise a challenging group to manage if concomitant NCCP is present. The patient’s prior history sets a precedent for future clinical evaluation and management. In one study, chest pain evaluated by cardiologists was clinically misdiagnosed as cardiac disease in 25% of patients (17). A number of previous studies have provided evidence that the reflux prevalence is over 40% in patients with CAD, with 40-70% of cases of reflux being directly associated with chest pain symptoms (18-23). However, this study is the first to investigate acid reflux in patients with CAD and refractory chest pain. In this study, we attempted to answer three questions: Is the chest pain and ischemic condition related to GERD? Does cardiac drug prescription predispose or aggravate
GERD? Can PPI therapy decrease ischemic events and improve the general HRQL of patients with CAD and GERD?

To answer the first question, we found that 49% of chest pain episodes occurred in association with acid reflux, while 15% of pain episodes coincided with both acid reflux and ST-segment shifts. These results are in line with previous observations. Garcia-Pulido et al. reported that 55% of patients with CAD have acid reflux, and 65% of those with acid reflux have chest pain related to acid reflux (18). Mehta et al. found that 49% of chest pain episodes are related to acid reflux in patients with CAD and that 20% of episodes coincide with reflux and ST-segment depression (24). Lux et al. showed that 57% of patients with CAD have chest pain correlated with acid reflux (20). Singh et al. investigated symptomatic coronary patients and found that 41% of such patients have acid reflux (21).

However, a more difficult task is to determine whether gastroesophageal reflux can actually provoke or worsen myocardial ischemia. A higher incidence (p=0.033) and longer duration (p=0.040) of ischemic events were observed in the GERD (+) patients in our study. This finding is also in concordance with previous observations. Caldwell et al. and Mellow et al. demonstrated such an association in laboratory settings (25, 26). Rosztóczy et al. also found that esophageal acid perfusion decreases the coronary flow velocity in 49% of patients with acid reflux episodes (27). However, clinical investigations concerning the influence of acid reflux on provoking myocardial ischemia have been conducted in only small groups of patients. For example, Singh et al. studied 34 symptomatic patients with CAD (21).

Mehta et al. investigated only 24 patients (24). There is only one investigation, performed by Dobrzycki et al. that studied 50 patients (28). However, the presence of PEAR was used to divide the groups into patients with and without GERD in that study. PEAR suggests the presence of GERD; however, establishing a temporal correlation between reflux events and chest pain is required to identify GERD as the source of chest pain (29). Therefore, the combination of PEAR and SI intuitively offers the best evidence for a GERD association.

This is the first study to assess the possible relationship between acid reflux and myocardial ischemia in patients with refractory chest pain in multiple ways. First, both PEAR and SI were used as GERD diagnosis criteria in this study. Second, the total time of pH <4 (%) and the number of all reflux episodes were used to measure the possible contribution of acid reflux to chest pain and ischemic events.

Having obtained data addressing the first question, we focused on the second question. It has been proven that common cardiac drugs used to treat CAD, particularly nitrates, calcium-channel blockers and antiplatelet drugs, may either predispose patients to GERD or aggravate preexisting GERD (7-9). However, we are the first to find that the combined use of common cardiac drugs, especially CCB combined with antiplatelets (p=0.014) and the combination of CCB, antiplatelets and nitrates (p=0.034), may predispose or aggravate GERD.

As to the third question, our study seems to have some clinical importance. We found that two-week PPI therapy not only restores a normal esophageal pH and reduces myo-
cardial ischemia, but also significantly improves the general HRQL in patients with CAD and GERD. This finding is in agreement with those of previous studies. Budzyński et al. reported that the double dose of omeprazole that is recommended as empirical therapy in patients with CAD significantly decreases the severity of symptoms in 35% of patients (30). Another study, performed by Liuazzo et al., demonstrated that concomitant esomeprazole therapy in patients with CAD and a history of atypical chest pain significantly reduces the percentage of patients experiencing chest pain (24.4% versus 54.8%; p<0.001). This study highlighted the possibility of improving an impaired HRQL in patients with CAD (31). Budzyński et al. completed a trial of the SF-36 survey in patients with CAD and recurrent angina-like chest pain. Improved HRQL scores in patients accepting PPI therapy were found in the survey (10). To investigate the patients’ overall state of health (physical, emotional and social), the SF-36 survey was also used as an HRQL instrument in our study. The improvements in some of the components of the SF-36 score after therapy with omeprazole observed in our subjects with CAD were similar to those observed in the study performed by Budzyński.

This study is associated with several limitations. First, our study was not placebo controlled. Because we knew that the patients with refractory chest pain also had acid reflux, we suggested that acid-reducing therapy may be helpful. This means that follow-up without acid-suppression therapy was not available, particularly after realizing the positive impact this therapy had on patient management. Furthermore, the small number of enrolled patients did not permit any randomized use of a placebo. However, all of the patients presented here were well-defined and homogenous. Second, the study investigated acid reflux only and not alkaline and/or air reflux. It is becoming clear that the esophageal and extraesophageal symptoms of GERD such as chest pain may also be associated with both acid reflux (esophageal pH 4-7) and non-acid reflux (2). However, previous studies have demonstrated that among the CAD patients experiencing chest pain, over 50% have acid reflux disease as the cause of noncardiac chest pain (3, 4). The role of non-acid gastroesophageal reflux in patients with CAD experiencing chest pain should be investigated in a future study. Third, CAD patients with refractory chest pain having angiographically intact coronary arteries were not included in this study, for example, patients with microvessel disease. For this special CAD group, significantly higher psychological scores on indices of anxiety and depression compared with patients with chest pain and angiographically proven CAD have been found in previous studies (32). In addition to obtaining endoscopic and/or pH monitoring evidence of GERD, further investigation of factors such as depression and anxiety disorders has been suggested (33). We plan to investigate this CAD group in our next study.

In conclusion, our study supports the hypothesis that gastroesophageal reflux is common in patients with CAD and refractory chest pain. Refractory chest pain in patients with CAD can be partially due to NCCP secondary to acid reflux. The combined use of common cardiac drugs, especially CCB combined with antiplatelets and the combination of CCB, antiplatelets and nitrates, may predispose CAD patients to GERD or aggravate preexisting GERD. Short-term PPI therapy therefore not only restores a normal esophageal pH, but also significantly improves the general HRQL in patients with CAD and GERD.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We would like to thank all members of the scientific education section of Suining Central Hospital and the physicians who were involved in planning and conducting the study. We also wish to thank the local health departments of the study area.

References


