Does acid reflux precipitate ischaemia in subjects with acute coronary syndrome?

Sunil K George, Boikhutso Tlou, Somalingum Ponnusamy, Datshana P Naidoo

Abstract

**Aim:** It has been postulated that gastro-oesophageal reflux disease (GORD) may trigger coronary ischaemia through viscerocardiac reflex vasoconstriction in subjects with ischaemic heart disease (IHD). Our aim was to estimate the prevalence of GORD in subjects with IHD who present with acute coronary syndrome (ACS) and to determine whether GORD may serve as a trigger for ischaemic events.

**Methods:** Twenty patients with isolated reflux oesophagitis and 39 with acute coronary syndrome (ACS with concomitant GORD) were studied. Twenty-two subjects comprising normal volunteers and those who were admitted for minor surgical trauma were used as normal controls. All subjects underwent oesophago-gastroduodenal endoscopy (EGD) and acid instillation with hydrochloric acid (0.1 M), as well as nuclear imaging (sestaMIBI) with technetium$^{99}$. Ischaemia was detected by ST depression using ECG monitoring for one hour during and immediately after EGD.

**Results:** Of the 111 subjects with ACS, 39 (35.1%) had erosive GORD and comprised the study group. Subjects with ACS had more incidence of diabetes ($p = 0.001$), hypertension ($p = 0.002$), a history of smoking ($p = 0.006$) and elevated serum triglyceride levels ($p = 0.008$) compared to the GORD group. Risk-factor clustering in the form of the metabolic syndrome was more common in ACS subjects (44 vs 5%; $p = 0.008$). ST depression was documented in 8/39 (20.5%) patients in the ACS group and 5/20 (25%) in the GORD group ($p = 0.958$). Reversible perfusion defects on sestaMIBI scan were seen in 35.6% of the ACS subjects.

**Conclusion:** Although GORD is common in subjects with ACS, we have not been able to show that GORD may serve as a trigger for ischaemia in these subjects.

**Keywords:** reflux oesophagitis, ischaemia, chest pain

Chest pain is one of the most frequent complaints in the emergency department and demands careful evaluation in order to determine the aetiology and institute appropriate care. Of all the chest pain syndromes, gastro-oesophageal reflux disease (GORD) is perhaps the most common, with prevalences ranging from two to 10% in Europe and 7% in America. Significant co-morbidity in the form of obesity often co-exists, with its associated complications such as erosive oesophagitis that frequently presents with heartburn and must be differentiated from cardiac ischaemia or myocardial infarction.

The epidemiology of GORD therefore requires further study in the ischaemic heart disease (IHD) population, including those presenting with acute chest pain. We examined the prevalence of GORD in subjects with acute coronary syndrome (ACS) and attempted to show whether GORD could precipitate ischaemia in these subjects.

**Methods**

Patients admitted to the coronary care unit (CCU) with a diagnosis of ACS were screened for the study. ACS was defined according to the criteria of Braunwald. Patients who were stable and pain free for at least three days were studied. Patients who were acutely ill or unstable, and those with renal impairment, left bundle branch block or known peptic ulceration were excluded. After obtaining informed consent, the subject was examined, bloods were sampled and the baseline electrocardiograph (ECG) was recorded. Parameters recorded included weight measured to the nearest 0.5 kg, and waist and hip circumferences as well as height according to standard guidelines. Risk factors were identified and categorised according to the presence/absence of the metabolic syndrome using the harmonised criteria. For the endoscopic procedure, after an overnight fast, subjects underwent oesophago-gastroduodenal endoscopy (EGD) and acid instillation. With the endoscope positioned just proximal to the esophageo-gastric junction, a volume of 60 ml of 0.1 M hydrochloric acid was administered over five minutes. The acid concentration was prepared by adding 5 ml of concentrated acid to 495 ml of deionised water. All EGD procedures were performed in the gastrointestinal (GI) unit by the author (SG) using a fibre-optic instrument (Olympus Evis 2000, Tokyo, Japan).
Two groups of subjects were included in the study to assess the effects of acid installation independent of concomitant ischaemia. Patients referred to the gastrointestinal unit at Addington Hospital with heartburn, who were diagnosed with erosive reflux oesophagitis at EGD, comprised the GORD group (Fig. 1). Subjects in whom the endoscopy was normal were also selected as normal control subjects. All subjects underwent acid instillation and Holter recording.

Informed consent was obtained from all individuals in the study and approval was granted by the bio-ethics committee of the Faculty of Health Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal.

Statistical analysis

Data analysis was conducted using SPSS (Statistical Packages for the Social Sciences) software (version 23). A p-value < 0.05 was deemed as statistically significant. A descriptive statistical analysis of the data (means and percentages) was initially conducted prior to inferential analysis. Proportions were used to estimate the prevalence of GORD in subjects with ACS. Difference in the proportions of ischaemia/infarction between study and control groups was analysed using the Pearson chi-squared test as well as determining whether the presence of GORD could trigger ischaemic events. Logistic regression was used to assess the odds of developing ST changes after acid instillation. Means for the groups were compared using one-way analysis of variance, followed by the Tukey post hoc test.

Results

A total of 376 patients underwent consecutive endoscopy. The 111 subjects with ACS were admitted to the CCU. They were stable and underwent endoscopy to determine the presence of oesophagitis (Fig. 1). Of these ACS subjects, 39 had grade A reflux oesophagitis and constituted the ACS study group.

Of the 265 patients with dyspepsia, 27 had GORD with grade A reflux oesophagitis. Seven of these subjects had either reversible (ischaemic) or fixed (infarct) changes on the sestaMIBI scan and were excluded, leaving 20 subjects with isolated GORD. None of the controls showed any reversible (ischaemic) or fixed (infarct) changes on the sestaMIBI scan, indicating they were also free of significant coronary artery disease.

There were 30 males and nine females (mean age 52 and 51 years, respectively) in the ACS group. These 39 subjects comprised 35 (89.7%) with ST-elevation myocardial infarction (MI) (45.7%) were in the inferior territory, 25.7% anterior and 28.6% lateral) and four (10.3%) subjects with non-ST-elevation MI.

There was no significant difference in the age distribution between ACS subjects and those with isolated GORD. There
was no difference in body mass index between the controls and ACS subjects \((p = 0.974)\) but waist measurements were lower in the control subjects \((p = 0.003; \text{GORD vs control} = 0.002)\) (Table 2).

As expected, risk-factor analysis revealed that incidence of diabetes mellitus, hypertension and smoking were more frequent in the ACS group. Control subjects were free of hypertension, hypercholesterolaemia and diabetes. Plasma glucose level was elevated in male subjects in both the ACS and GORD groups, but was normal in the controls \((p < 0.001)\). Risk-factor clustering in the form of the metabolic syndrome was present in 17/39 (44%) in the ACS group, 1/20 (5%) in the GORD group and none in the control group.

All subjects had grade A oesophagitis in both the ACS and the GORD group. There was no chest pain on acid instillation among the subjects with isolated GORD and the controls. Mild retrosternal chest pain developed in two subjects in the ACS group but this was short lived and did not require nitroglycerin, nor was it associated with ECG changes.

During acid installation, ECG recording showed 8/39 (20.5%) subjects. No differences were observed in ST changes between ACS and GORD \((p = 0.010)\) and GORD vs control \((p = 0.014)\) subjects. No differences were observed in ST changes between ACS and GORD \((p = 0.958)\) subjects.

### Table 2. Demographic data and baseline risk-factor profile

<table>
<thead>
<tr>
<th></th>
<th>ACS ((n = 9))</th>
<th>GORD ((n = 14))</th>
<th>Control ((n = 8))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52 ± 7.9</td>
<td>51 ± 9.0</td>
<td>49 ± 9.0</td>
<td>49 ± 12.0</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>93 ± 9.0</td>
<td>93.7 ± 1.9</td>
<td>94.9 ± 9.5</td>
<td>96.0 ± 1.8</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>2.2 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>2.3 ± 0.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 2.2</td>
<td>24.7 ± 4.0</td>
<td>25.8 ± 5.5</td>
<td>28.4 ± 5.5</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>122 ± 17 (39)</td>
<td>123 ± 17 (43.6)</td>
<td>20 ± 15 (51.2)</td>
<td>20 ± 15 (51.2)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>74 ± 7</td>
<td>74 ± 9.3</td>
<td>71 ± 5.7</td>
<td>65 ± 6.0</td>
</tr>
<tr>
<td>Plasma glucose</td>
<td>5.8 ± 0.9</td>
<td>7.9 ± 3.4</td>
<td>4.3 ± 5.2</td>
<td>4.5 ± 0.61</td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>6.9 ± 5.0</td>
<td>5.9 ± 2.5</td>
<td>5.1 ± 4.9</td>
<td>5.1 ± 0.9</td>
</tr>
<tr>
<td>Serum HDL-C (mmol/l)</td>
<td>1.0 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 1.1</td>
<td>1.1 ± 0.2</td>
</tr>
<tr>
<td>Serum LDL-C (mmol/l)</td>
<td>2.6 ± 3.0</td>
<td>3.0 ± 1.2</td>
<td>2.3 ± 2.2</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>2.2 ± 1.7</td>
<td>2.0 ± 0.3</td>
<td>1.4 ± 1.2</td>
<td>1.4 ± 0.2</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; GORD, gastro-oesophageal reflux disease; F, female; M, male; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Figures in brackets denote percentages.

### Table 3. ST changes after acid instillation

<table>
<thead>
<tr>
<th>ST depression</th>
<th>ACS ((n = 39))</th>
<th>GORD ((n = 20))</th>
<th>Control ((n = 22))</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>3 (7.7)</td>
<td>4 (20)</td>
<td>0</td>
<td>0.958</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5 (12.8)</td>
<td>1 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>8 (20.5)</td>
<td>5 (25)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Compared to the controls, ST changes were more frequently recorded in ACS \((p = 0.010)\) and GORD \((p = 0.014)\) subjects. No differences were observed in ST changes between ACS and GORD \((p = 0.958)\) subjects.

ACS, acute coronary syndrome; GORD, gastro-oesophageal reflux disease.
similar prevalence rates for GORD in patients with IHD.\textsuperscript{22,24,27} In described even during treadmill testing.\textsuperscript{19} Since the prevalence of pain that mimics angina pectoris. This phenomenon has been reflux may occur during exercise and cause exertional chest has been shown that as many as 50\% of patients with cardiac ailments may co-exist and interact to precipitate ischaemia. It 

Table 4. Prevalence of ventricular arrhythmias (Lown grade)  

<table>
<thead>
<tr>
<th>Grade</th>
<th>ACS (n = 39)</th>
<th>GORD (n = 20)</th>
<th>Control (n = 22)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, n (%)</td>
<td>11/39 (28.2)</td>
<td>15/20 (75)</td>
<td>14/22 (64)</td>
<td></td>
</tr>
<tr>
<td>1, n (%)</td>
<td>21/39 (53.8)</td>
<td>4/20 (20)</td>
<td>8/22 (36)</td>
<td></td>
</tr>
<tr>
<td>2, n (%)</td>
<td>3/39 (7.7)</td>
<td>1/20 (5)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3, n (%)</td>
<td>3/39 (7.7)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4, n (%)</td>
<td>1/39 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Significant Lown grade arrhythmias. Lown 3 (p < 0.001) and Lown 4 (p = 0.001) were more frequent in ACS compared to GORD subjects and controls after acid instillation.

Discussion

It is estimated that about 30\% of subjects undergoing coronary angiography in the USA have normal epicardial coronary arteries and in these individuals, oesophageal diseases may account for the symptoms in 18 to 56\%.\textsuperscript{26} Chest pain arising from the oesophagus may be indistinguishable from angina pectoris, since both conditions share the same nerve plexuses for their innervation.\textsuperscript{18} The problem is compounded by the fact that gastro-oesophageal reflux may occur during exercise and cause exertional chest pain that mimics angina pectoris. This phenomenon has been described even during treadmill testing.\textsuperscript{19} Since the prevalence of cardiac ischaemia are typically effort-induced pain that radiates to the arm and is relieved by rest and nitroglycerin. However, it is documented that relief with sublingual nitroglycerin is not limited to a pain of coronary origin,\textsuperscript{97} making it difficult for the clinician to distinguish between the two conditions when symptoms overlap. While it may complicate symptomatology in subjects with acute coronary syndrome,\textsuperscript{19} there is increasing evidence that GORD may also precipitate cardiovascular events,\textsuperscript{9} particularly since both conditions share the same nerve plexuses for their innervation.\textsuperscript{19}

The clinical history does not always enable a physician to distinguish accurately between cardiac and oesophageal causes of chest pain. Symptoms suggestive of cardiac ischaemia are typically effort-induced pain that radiates to the arm and is relieved by rest and nitroglycerin. However, it is documented that relief with sublingual nitroglycerin is not limited to a pain of coronary origin,\textsuperscript{97} making it difficult for the clinician to distinguish between the two conditions when symptoms overlap. While it may complicate symptomatology in subjects with acute coronary syndrome,\textsuperscript{19} there is increasing evidence that GORD may also precipitate cardiovascular events,\textsuperscript{9} particularly since both conditions share the same nerve plexuses for their innervation.\textsuperscript{19}

This study showed a 35.1\% prevalence of erosive GORD in patients with recent ACS, which is in keeping with other studies that have shown prevalence rates varying from 39 to 53\%.\textsuperscript{21,25} Only one study by Battaglia et al.\textsuperscript{16} has yielded a much lower prevalence.\textsuperscript{26}

Studies using pH monitoring have documented consistently similar prevalence rates for GORD in patients with IHD.\textsuperscript{22,24,27} In a study of 51 patients with coronary artery disease, Rosztóczy et al.\textsuperscript{16} reported a 45\% prevalence of GORD using pH monitoring and manometry.\textsuperscript{27} Similarly, Svensson et al.\textsuperscript{2} found a prevalence of 42\% on manometry.\textsuperscript{2} Myocardial perfusion imaging and oesophageal scintigraphy have also shown a 39\% prevalence of both oesophageal dysfunction and IHD.\textsuperscript{23} Whatever the modality used to detect GORD, it is apparent that at least one-third of subjects with IHD have concomitant GORD.

In this study we determined whether GORD could precipitate ischaemia and used acid instillation during EGD as a surrogate for acid reflux.\textsuperscript{24} In our study, 20.5\% of patients with ACS + GORD developed ST depression on ECG monitoring shortly (within five minutes) after acid instillation. Two studies similar to ours have observed that eight\textsuperscript{27} and 27\%\textsuperscript{28} of subjects with GORD and co-existing IHD developed ST changes after acid installation. In our study, we documented similar ST changes in the group with isolated GORD who did not have coronary disease, as demonstrated on sestaMIBI scanning, and were therefore unable to conclude that these changes were indicative of ischaemia.

Lam et al.\textsuperscript{29} looked at 30 patients with angiographic evidence of IHD admitted to the CCU with angina.\textsuperscript{29} Their 24-hour ECG and pH recordings showed that chest pain was preceded by a drop in pH in only one patient. Based on such findings, Lam et al.\textsuperscript{29} and Valori\textsuperscript{29} are also doubtful of the existence of the link between GORD and ischaemic heart disease. Several authors have suggested that the development of ST changes and the documentation of ischaemia in these subjects during acid installation is probably coincidental,\textsuperscript{29,30} whereas other researchers have postulated the existence of an oesophageo-cardiac reflex resulting in linked angina\textsuperscript{30,31} precipitated by acid reflux.

The mechanisms for the development of ST changes in subjects with GORD and IHD have not been clearly established and are possibly due to a combination of factors. In Rosztóczy’s study of 51 patients, ST changes occurred in patients with epicardial and microvascular disease, as well as in those with a negative cardiological evaluation. This suggests that the infarct territory is not a factor in the development of ST changes.\textsuperscript{32} Recently Hui et al.\textsuperscript{32} suggested that oesophageal pain could result in myocardial ischaemia via an adrenergic stimulus, resulting in increased myocardial oxygen demand. Alternatively, he postulated that oesophageal pain could trigger the oesophageo-cardiac reflex, resulting in coronary vasconstriction and decreased myocardial oxygen supply.

The explanation for ischaemic ST changes developing in our subjects with isolated GORD cannot be explained, since these subjects did not have coronary disease, as demonstrated on sestaMIBI scans. The possibility that the ECG changes could have been induced by the procedure itself is unlikely, since no such ST changes were documented in the normal control group who did not have GORD or IHD.

Chauhan et al.\textsuperscript{33} proposed a possible mechanism for ST changes developing in subjects without IHD on the basis of microvascular vasocostriction, as demonstrated by a reduction in coronary blood flow following acid instillation in subjects with syndrome X and normal coronary arteries.\textsuperscript{33} They suggested that these microvascular changes could be mediated via the same neural reflex or the release of vasoactive substances following acid installation. Since ST changes on acid installation occurred in subjects with coronary syndrome X but not in transplant recipients (denervated hearts), Chauhan and co-workers concluded that ST changes were due to a viscerocardiac reflex. A significant finding in our study was the high prevalence of the metabolic syndrome in the ACS patients, and to some extent in the isolated GORD subjects, indicating that a few patients with GORD were also insulin resistant. The association of microvascular disease with syndrome X and the metabolic syndrome\textsuperscript{34} might explain the development of ischaemic ST changes via the oesophageo-cardiac reflex, which is thought to increase microvascular resistance, potentially resulting in myocardial ischaemia.\textsuperscript{34} Microvascular disease is an established
cause of myocardial ischaemia in the absence of epicardial disease. Although our findings may indicate the presence of underlying microvascular disease in association with the metabolic syndrome, which we documented in both the GORD and ACS subjects, a more plausible explanation could be that the ST changes documented during acid installation were a false-positive finding, unrelated to the presence of ischaemia, or a reflex phenomenon that does not necessarily indicate ischaemia.

An advantage of our study is that oesophageal assessment was done using fibre-optic endoscopy and only patients with erosive oesophagitis were selected for the study. A limitation of earlier studies was that endoscopy was not performed to assess the oesophageal lesion. Evidence of erosive oesophagitis on endoscopy provides macroscopic evidence of oesophagitis that is graded by internationally accepted criteria. According to Saltissi and Rosztóczy et al., ST changes are more likely to develop in a diseased oesophagus (e.g. with GORD) due to pre-sensitisation of pain receptors.

A possible limitation of our study is related to the selection of GORD subjects, all of whom had grade A oesophagitis. It is thought that severe oesophagitis associated with ulceration (grade C onwards), tissue damage and inflammation might have been a more potent trigger stimulating the viscerocardiac reflex resulting in ST changes. Furthermore, it may also be argued that oesophageal acid instillation is non-physiological, with effects distinctly different from symptoms experienced in oesophageal reflux disease. Single, short episodes of acid installation might not have produced significant ST changes of ischaemia since the acid infusion in our study was for a duration of five minutes. Over a 24-hour period, multiple episodes of reflux might occur, possibly reaching the threshold for triggering ischaemia. Higher rates of acid-induced chest pain (25 and 68%) have been reported in studies by Davies et al. and Tougas et al. where infusion was for 10 and 20 minutes, respectively, and associated with a reduction in the threshold for angina.

There are other limitations that need to be considered in evaluating the results of this study. The first consideration relates to the sample size. The study recruited 39 subjects with ACS, of whom 14 had reversible ischaemia on sestaMIBI. Since the development of ST changes is more likely to occur in subjects with reversible ischaemia in comparison to subjects with completed infarcts (and no residual ischaemia), a larger sample of subjects with reversible ischaemia would have been more appropriate. Furthermore, ECG monitoring was only conducted for a period of one hour after acid instillation.

This study has clinical implications in the approach to subjects with retrosternal chest pain symptoms. Reliance on the chest pain characteristics is often difficult in subjects with dual pathology (GORD plus IHD), often rendering symptoms atypical. In non-acute subjects, non-invasive testing with sestaMIBI is helpful for the detection of coronary artery disease and requires treatment on an individual basis. The development of ST changes in subjects with recent ACS and a history of GORD is much more imminent and has immediate prognostic implications for the management of significant ischaemia and should be addressed on an individual basis. Such patients need immediate endoscopy to detect and stage GORD in order to evaluate the risk of bleeding in subjects receiving antiplatelet therapy.

In subjects with GORD the presence of cardiovascular risk factors in association with ST changes should alert the clinician to co-existing coronary artery disease. In the absence of epicardial coronary disease, the possibility of microvascular disease should be considered in subjects with the metabolic syndrome and their risk factors addressed. Proton pump inhibitors should be considered as part of the treatment in patients where myocardial ischaemia co-exists with GORD as they are more prone to cardiovascular events.

**Conclusion**

We have shown that at least one-third of our ACS patients had concomitant GORD, which was probably related to the high prevalence of obesity in these subjects. While we are unable to conclude that GORD may serve as a trigger for ischaemia in subjects with ACS, the high prevalence of the metabolic syndrome in these subjects suggests the possibility of underlying microvascular disease.

**References**


39. Saltissi S. Cardio-oesophageal reflex and ‘linked angina’ – is the way to a man’s (or woman’s) heart through the stomach? *Heart* 1996; 79: 325–330.