Towards better understanding of symptoms associated with disordered esophageal function
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DETERMINANTS OF THE ASSOCIATION BETWEEN NON-CARDIAC CHEST PAIN AND REFLUX

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ABSTRACT

Background
Gastroesophageal reflux is considered to be the most common gastrointestinal cause of non-cardiac chest pain (NCCP). It remains unclear why some reflux episodes in the same patient cause chest pain while others do not. To understand more about the mechanisms by which reflux elicits chest pain, we aimed to identify factors which are important in triggering chest pain.

Methods
In this multicenter study, 120 patients with NCCP were analyzed using 24-hour pH-impedance monitoring. In the patients with a positive association between reflux and chest pain, the characteristics of the reflux episodes which were followed by a chest pain episode were compared with reflux episodes that were not associated with chest pain.

Results
Using 24-hour pH-impedance monitoring, 40% of the NCCP patients were identified as having reflux as a possible cause of their chest pain. Reflux episodes that were associated with chest pain had a higher proximal extent (p=0.007), a higher volume clearance time (p=0.030), were more often acidic (p=0.011), had a lower nadir pH (p=0.044) and had a longer acid duration time (p=0.027) than reflux episodes which were not followed by chest pain. Patients who experienced typical reflux symptoms were more likely to have reflux as the cause of their chest pain (52% vs 31.4%, p=0.023).

Conclusions
The presence of a larger volume of acid refluxate for a longer period of time appears to be an important determinant of perceiving a reflux episode as chest pain. 24-hour pH-impedance monitoring is an important tool in identifying gastroesophageal reflux as a potential cause of symptoms in patients with NCCP.
INTRODUCTION

Non-cardiac chest pain (NCCP), defined as recurrent retrosternal chest pain which remains unexplained after a cardiac workup, is a common disorder with a prevalence of 13% up to approximately 25%\(^1,2\). NCCP significantly impairs the health-related quality of life\(^3\), and is a significant burden to society due to the work absenteeism and the healthcare seeking attitude\(^1,4\). NCCP can be the result of gastroesophageal reflux disease (GERD), esophageal dysmotility, psychiatric disease such as panic attacks, and musculoskeletal disorders\(^5\). GERD is the most common gastrointestinal cause of NCCP\(^6\), with many studies showing an association between NCCP and GERD\(^2,7,8\). As a result, assessing the presence of GERD is an important step in the evaluation of patients with NCCP. Upper endoscopy is considered to have a limited value in NCCP patients due to the low prevalence of mucosal findings. Ambulatory pH-impedance monitoring can play a pivotal role in the work-up.

Ascertaining that GERD is the cause of chest pain is valuable in patients with NCCP as this allows for appropriate management of the symptoms, prevents further unnecessary testing and may reduce some of the functional disability caused by undiagnosed chest pain\(^7\). It is important to note that the relationship between gastroesophageal reflux and NCCP is complex. Using ambulatory pH-impedance monitoring a pathological esophageal acid exposure time (AET) can be detected\(^7,9\). Even though a diagnosis of GERD based on a pathological AET does not establish a causal relationship between reflux and chest pain, treating NCCP patients with a pathological AET with proton pump inhibitors (PPIs) results in a relief of symptoms in up to 78% of patients\(^10\). The symptom association probability (SAP)\(^11\) can be used to evaluate whether a temporal association between reflux events and chest pain episodes is found more often than by chance alone. It has been demonstrated that a positive result of statistical tests of the symptom-reflux association predicts the outcome of antireflux therapy\(^12\).

Several questions concerning reflux-induced chest pain have remained unanswered. For instance, it is unclear why reflux causes heartburn in some patients and chest pain in others. In patients with GERD and typical reflux symptoms, reflux episodes are more likely to cause heartburn or regurgitation when they have a higher proximal extent, a lower nadir pH, a larger pH drop and a longer volume and acid clearance time\(^13,14\). These studies have increased our understanding of the perception of reflux, yet it remains unclear why some reflux episodes in the same patient cause chest pain while others do not. Therefore, in this study we aimed to explore the factors that determine whether reflux will be followed by chest pain.
METHODS

Patients
We analyzed the 24-hour ambulatory pH-impedance studies that were performed in 120 patients with non-cardiac chest pain, between 01-2011 and 01-2017, in two different tertiary care centers in the Netherlands; the Academic Medical Center (AMC) in Amsterdam, and the University Medical Center in Utrecht. Patients were recruited through the gastroenterology outpatient clinics and esophageal function labs of these two hospitals. Esophageal chest pain was defined as midline chest pain or discomfort not of burning quality which had not been diagnosed as due to ischemic heart disease by a physician. Retrosternal pain had to be the dominant symptom in all patients and a cardiac cause had to have been excluded or deemed extremely unlikely. If eosinophilic esophagitis was suspected, further diagnostic testing was performed to rule this out. Proton pump inhibitors were stopped at least 7 days prior to the measurements and drugs affecting gastro-intestinal motility or secretion were stopped at least 3 days prior to the measurements. Patients were excluded if they had undergone any upper gastro-intestinal surgery. The presence of typical reflux symptoms (heartburn and/or regurgitation) was assessed by retrospectively reviewing the referral letter and clinicians’ notes. Patients underwent esophageal manometry prior to the 24-hour pH-impedance measurement to provide information on the position of the lower esophageal sphincter (LES) for the correct placement of the pH-impedance catheter and to rule out significant motility disorders such as achalasia. The study proposal was submitted to the local institutional review board of the Academic Medical Center in Amsterdam, the Netherlands, and formal evaluation was waived according to Dutch law.

Ambulatory 24-hour pH-impedance monitoring
All subjects underwent ambulatory 24-hour pH-impedance monitoring which was carried out using a combined pH-impedance catheter assembly (Unisensor AG, Attikon, Switzerland). The catheter consisted of six impedance recording segments which were located at 2-4, 4-6, 6-8, 8-10, 14-16 and 16-18 cm above the upper border of the LES, and one ion-sensitive field-effect transistor pH electrode which was positioned 5 cm above the upper border of the manometrically localized LES. The pH and impedance signals were stored on a digital datalogger (Ohmega, MMS, Enschede, the Netherlands) using a sampling frequency of 50 Hz.

Patients were instructed to press the event marker button on the pH data logger whenever they experienced symptoms and were requested to note down the nature of the symptom event and its time of onset in a specially designed diary. In addition, patients had to mark the times of meals and beverages in the diary and were instructed to restrict their intake to three meals and four beverages at standardized
times throughout the 24 hours. Patients were encouraged to maintain their normal daily activities throughout the measurement and had to mark the period spent in the supine position.

**Data analysis**

The pH-impedance recordings were uploaded to a computer and were then manually analyzed using commercially available software (MMS, Enschede, the Netherlands).

**Reflux detection**

Gastroesophageal reflux was defined as an orally progressing drop in impedance to <50% of the baseline values, starting at the most distal impedance segment (located 2-4 cm above the LES) and propagating retrogradely to at least the next impedance segment (4-6 cm above the LES). If the pH fell below 4 for at least 4 seconds, then the reflux episode was defined as acidic. If the pH was already below 4 at onset of the reflux episode, then a further drop in pH of at least 1 unit for at least 4 seconds was required. A reflux episode was defined as weakly acidic if the drop in impedance was not accompanied by a drop in pH below 4.

Mixed reflux was defined as gas reflux (rapid (>3000 Ω/s) retrograde moving increase in impedance in at least two consecutive impedance segments) occurring immediately before or during liquid reflux. In a subset of the patients, a detailed analysis of each reflux episode was made in which the proximal extent, the ascending velocity, the nadir pH and the change in pH was noted. The acid clearance time was defined as the time in seconds from the moment the pH dropped below 4 until it recovered to a value of 4 or until a new reflux episode started. If the pH was already below 4 at the start of the reflux episode, then a drop of 1 pH indicated the start. The volume clearance time was defined as the duration in seconds from the 50% drop in impedance of baseline in the most distal segment until the impedance recovered to above this point again. The acid duration time was defined as the duration in seconds with a pH below 4. The total acid exposure time, defined as the percentage of time that the pH was below 4 throughout the entire measurement, and the total number of reflux events (both acidic and weakly acidic) were calculated for each patient. The total distal acid exposure time was considered to be pathological if it was greater than 6% of the total recording time.

**Association between reflux and symptoms**

A reflux episode was considered to be associated with a typical reflux symptom (heartburn and/or regurgitation) or with chest pain if the symptom followed within two minutes after the onset of the reflux episode. We used the SAP to assess the association between reflux episodes and symptoms. A SAP greater than 95% was considered to be statistically significant. If symptoms occurred outside of
the two-minute time window following the onset of a reflux episode, then they were considered unrelated to that reflux episode. Figure 1 shows an example of a reflux-associated chest pain episode.

**Statistical analysis**

This was a retrospective analysis of a prospectively constructed database. Statistical analyses were performed using SPSS version 22 (SPSS, Inc. Chicago, IL, USA). Data are presented as median (interquartile range (IQR)). Patient groups were compared using the Mann-Whitney U-test. Proportions were compared using the chi-squared test. The Fisher exact test was used to calculate the SAP. The Wilcoxon signed rank test was used to compare reflux episodes which were associated with chest pain with non-associated reflux episodes in subjects with a positive SAP for reflux-associated chest pain. Relationships between parameters were expressed using the Spearman’s Rank correlation. A p-value < 0.05 was considered to be statistically significant.

**Figure 1.** Example of a reflux-chest pain sequence recorded during concurrent measurement of pH and impedance. The impedance signal shows a retrograde drop consistent with liquid reflux, and in the pH signal an acid reflux event can be seen.
RESULTS

Patient population
One-hundred and twenty patients (56.7% female, median age 54 years) with non-cardiac chest pain were evaluated with ambulatory 24-hour pH-impedance monitoring. In all patients, a cardiac origin of the pain was ruled out prior to the 24-hour study. The main patient characteristics are shown in table 1. A total of 63 patients (52.5%) experienced typical reflux symptoms (heartburn and/or regurgitation) in addition to their chest pain.

Gastroesophageal reflux
In total, 4057 reflux episodes were detected using 24-hour pH-impedance monitoring, of which 3067 (75.6%) were acidic and 990 (24.4%) were weakly acidic. A median of 31 (19-44) reflux episodes were found per patient, with 23 (11-37) acidic and 7 (4-10) weakly acidic.

Forty-two patients (35%) had a pathological acid exposure time. A median esophageal acid exposure time of 3.9% (1.2-7.9) was found with 5.3% (1.7-10.8%) in the upright position and 0.1% (0-2.5) in the recumbent position.

Association between reflux and symptoms
Fifty patients (41.7%) reported typical reflux symptoms (heartburn and/or regurgitation) during the 24-hour pH-impedance measurement. A total of 340 typical reflux symptoms were reported, of which 198 were associated with a reflux episode (176 acidic and 22 weakly acidic). In 25 patients (20.8%) a positive SAP was found for the association between reflux episodes and typical reflux symptoms. Patients who experienced at least one typical reflux symptom during the 24-hour measurement had significantly more often a pathological acid exposure time (48% vs 25.7%, p=0.012), and had significantly more often a positive association between reflux and chest pain.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>120</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>54</td>
</tr>
<tr>
<td>Female gender</td>
<td>68 (56.7%)</td>
</tr>
<tr>
<td>Number of patients presenting symptoms</td>
<td></td>
</tr>
<tr>
<td>Retrosternal pain</td>
<td>120 (100%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>59 (49.2%)</td>
</tr>
<tr>
<td>Regurgitation</td>
<td>29 (24.2%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>16 (13.3%)</td>
</tr>
</tbody>
</table>
(20% vs 7.1%, p=0.036). As a result, these patients with at least one typical reflux symptom were more likely to end up having reflux as a cause of their chest pain than patients without typical reflux symptoms (52% vs 31.4%, p=0.023).

One-hundred and three patients (85.8%) reported chest pain symptoms during the 24-hour pH-impedance measurement. A total of 517 chest pain symptoms were registered (median of 2.5 (1-6)), of which only 88 (17.0%) were associated with a reflux episode. Out of the 88 associated chest pain symptoms, only 13 were associated with weakly acidic reflux. In only 15 patients (12.5%) a positive SAP was found for the association between reflux episodes and chest pain symptoms. If weakly acidic reflux episodes had not been used in the analysis, only 1 out of the 15 patients would not have had a positive SAP. Patients who experienced at least one chest pain symptom during the 24-hour measurement had significantly more acid reflux episodes (25 (15-37) vs 11 (4.5-31.5), p=0.042), had a significantly higher total acid exposure time (4.7% (1.5-8.1) vs 1.8% (0.6-3.4), p=0.025), and had significantly more often a pathological acid exposure time (38.8% vs 11.8%, p=0.030), compared to patients who did not experience chest pain symptoms. Ten out of the 15 patients with a positive association between reflux and chest pain also experienced typical reflux symptoms during the 24-hour measurement.

A total of 48 patients (40%) had a pathological acid exposure time and/or a positive association between reflux and chest pain. Six out of the 15 patients with a positive SAP for reflux-associated cough did not have a pathological acid exposure time.

Reflex episodes associated with chest pain versus not associated reflux episodes
In 15 patients, a positive SAP was found for reflux-associated chest pain. In these patients, 55 reflux episodes were associated with chest pain episodes and 546 reflux episodes were not. Out of the 55 chest pain-associated reflux episodes, 6 (10.9%) were weakly acidic. In table 2 the characteristics of the reflux episodes which were associated with chest pain are compared to those which were not.

As shown in Figure 2, the proximal extent was significantly higher (p=0.007) in the chest pain-associated reflux episodes. Per patient, a median of 6 reflux episodes reached the most proximal impedance sensor. Only 11.5% of all reflux episodes reaching the most proximal sensor were associated with chest pain. However, 22 (40%) of the 55 reflux episodes which were associated with chest pain episodes reached the most proximal sensor. In addition, we found that the nadir pH was significantly lower in the reflux episodes which were associated with chest pain than in the non-associated episodes (p=0.044), and the acid duration time was significantly longer (p=0.027). Moreover, reflux episodes which were associated with chest pain also had a significantly longer volume clearance time (p=0.030) and were significantly more often acidic (p=0.011). No significant difference was found for the ascending velocity, the magnitude of the pH drop, or the acid clearance time. A correlation was
found between the proximal extent of the refluxate and the volume clearance time ($r=0.538$, $p=0.039$).

Table 2. Characteristics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Reflux episodes associated with chest pain</th>
<th>Reflux episodes not associated with chest pain</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal extent (cm)</td>
<td>15 (15-17)</td>
<td>9 (9-15)</td>
<td>0.007</td>
</tr>
<tr>
<td>Ascending velocity (cm/s)</td>
<td>2.2 (1.7-3.0)</td>
<td>3 (2.3-4)</td>
<td>0.460</td>
</tr>
<tr>
<td>Nadir pH</td>
<td>1.7 (1.2-2.1)</td>
<td>2 (1.5-2.6)</td>
<td>0.044</td>
</tr>
<tr>
<td>pH drop</td>
<td>3.7 (2.3-4.5)</td>
<td>3.5 (2.8-3.9)</td>
<td>0.551</td>
</tr>
<tr>
<td>Volume clearance time (s)</td>
<td>17 (11-33)</td>
<td>11 (10-15)</td>
<td>0.030</td>
</tr>
<tr>
<td>Acid duration time (s)</td>
<td>101 (38-223)</td>
<td>50 (22-93)</td>
<td>0.027</td>
</tr>
<tr>
<td>Acid clearance time (s)</td>
<td>109 (49-223)</td>
<td>63 (53-115)</td>
<td>0.140</td>
</tr>
<tr>
<td>Percentage acidic (%)</td>
<td>100 (100-100)</td>
<td>86 (79-92)</td>
<td>0.011</td>
</tr>
<tr>
<td>Percentage liquid (%)</td>
<td>50 (33-100)</td>
<td>47 (31-61)</td>
<td>0.530</td>
</tr>
</tbody>
</table>

Reflux episodes which were associated with chest pain are compared to reflux episodes which were not associated with chest pain. All values are shown as median (IQR). The p-value was calculated using the Wilcoxon signed rank test.

Figure 2. Boxplot graph comparing the proximal extent of the reflux episodes which were associated with chest pain compared with reflux episodes which were not.
DISCUSSION

The relation between gastroesophageal reflux and chest pain is complex. Gastroesophageal reflux is an important factor in NCCP, yet it remains unclear why some patients with gastroesophageal reflux present with chest pain while others do not. The results of our study corroborate the importance of 24-hour pH-impedance monitoring in NCCP patients, and our study is the first to assess a wide range of reflux characteristics in patients with a temporal association between reflux and chest pain.

Previous studies have found that the proximal extent of the refluxate, the nadir pH, the magnitude of the pH drop, and the acid clearance time are all important for the perception of typical reflux symptoms. As a result, it has become clear that the acidity of the refluxate is an important determinant of the perception of typical reflux symptoms. Interestingly, we recently demonstrated that the acidity of the refluxate seems to be less relevant in patients with reflux-induced chronic cough. In the reflux-cough syndrome, the volume of the refluxate and the esophageal exposure time to refluxate were found to be important. In the present study, we compared chest pain-associated reflux episodes with pain-free reflux episodes in patients with a positive association for reflux-associated chest pain. In accordance with studies evaluating the perception of the typical reflux symptoms, we found the acidity of the refluxate to be an important factor in perceiving a reflux episode as chest pain as significantly more reflux episodes which were associated with chest pain were acidic. Moreover, the nadir pH was significantly lower and the acid duration time was significantly longer in the reflux episodes associated with chest pain. This suggests that not only the degree of acidity is important in perceiving a reflux episode as chest pain, but also the duration that the acid is present in the esophagus.

The importance of the acidity is further supported by the finding that patients who experienced chest pain during the 24-hour measurement, irrespective of a positive association, had significantly more acid reflux episodes, a significantly higher percentage total acid exposure time and significantly more often a pathological acid exposure time compared to patients who did not experience chest pain. These findings can help explain why previous studies found that treating a pathological acid exposure time, even without evaluating for an association between reflux and chest pain, results in a relief of symptoms in up to 78% of patients. In our study, 40% of the patients had a pathological acid exposure time and/or a positive association between reflux and chest pain. Previous studies considered GERD as a possible cause of NCCP when a pathological acid exposure time was detected or a relationship between reflux episodes and chest pain was found. Therefore, in 40% of our patients GERD could be the cause of the chest pain, demonstrating the importance of performing a 24-hour pH-impedance measurement. Thirty-five percent of our patients had a pathological acid exposure time which is less than reported by previous studies. The difference could be explained by a difference in criteria of what is considered as a pathological...
acidity exposure time. Whilst we used a more stringent cutoff value of 6% in our study, some other studies used 4% as a cutoff.

Only a minority of the NCCP patients (12.5%) had a positive temporal association between reflux and chest pain. This could in part be explained by the low number of chest pain episodes reported by the patients\textsuperscript{21}, which in our study was 2.5 per 24-hour measurement per patient. Nevertheless, a temporal association between reflux events and chest pain makes it more likely that the pain can be attributed to GERD than merely the presence of a pathological acid exposure time. Moreover, 6 out of the 15 patients with a positive association did not have a pathological acid exposure time, demonstrating that the presence of a high distal esophageal acid exposure is not necessary for a patient to perceive chest pain symptoms. In other words, if only acid exposure were evaluated, a reflux origin of the chest pain would have been missed in 40% of these patients. The clinical relevance of reflux-symptom association testing is supported by the finding that positive statistical indices of symptom association help predict therapeutic success in NCCP patients\textsuperscript{12}.

Not only the acidity but also the spread of the refluxate through the esophagus was found to be important in perceiving a reflux episode as chest pain. We found that the proximal extent of the refluxate was significantly higher in the reflux episodes which were associated with chest pain compared to those which were not. Moreover, 40% of the chest pain-associated reflux episodes reached the most proximal sensor, demonstrating the importance of proximal extent as a determinant of reflux-associated chest pain. Nevertheless, it is important to point out that most of the reflux episodes reaching the most proximal sensor did not trigger chest pain. Furthermore, the number of reflux episodes reaching the most proximal sensor did not differ from healthy subjects\textsuperscript{22}. This suggests that the perception of chest pain is not linked to an increased number of reflux episodes reaching the most proximal sensor, but rather that these reflux episodes are more likely to be perceived. Increased reflux sensitivity in the proximal esophagus may be related to increased acid exposure of the distal esophagus. It has been shown that infusion of hydrochloric acid into the distal esophagus over 30 minutes lowers the pain threshold to electrical stimulation in the upper esophagus\textsuperscript{23}.

We also found a significantly higher volume clearance time in reflux episodes associated with chest pain compared to those which were not. Moreover, the volume clearance time correlated well with the proximal extent. This suggests that the volume of the refluxate is an important determinant for the perception of a reflux episode as chest pain. Therefore it seems that the presence of a large volume of acid refluxate for a longer period of time plays a major role in perceiving a reflux episode as chest pain. It is possible that a larger volume is more easily perceived due to a larger esophageal distension caused by the refluxate as previous studies have shown that balloon distension is perceived at lower volumes in patients with NCCP than in healthy subjects\textsuperscript{24-27}. Moreover, the importance of acid has also been highlighted by a study
showing that perception is increased when balloon distension is preceded by acid infusion in comparison to saline.27

Approximately half of our patients experienced typical reflux symptoms, with 50 patients (41.7%) also reporting typical reflux symptoms during the 24-hour measurement. Patients who experienced at least one typical reflux symptom during the 24-hour measurement had significantly more often a pathological acid exposure time and had significantly more often a positive association between reflux and chest pain. Moreover, two-thirds of the patients with a positive association between reflux and chest pain also experienced typical reflux symptoms during the 24-hour measurement. This is in line with previous findings that NCCP patients who also experience typical reflux symptoms are more likely to have GERD be considered the cause of their chest pain.20,28

In conclusion, 24-hour pH-impedance monitoring is an important tool in identifying GERD as a potential cause of symptoms in patients with NCCP. The results of our study indicate that not only the acidity of the refluxate, but also the proximal extent and volume clearance time are important determinants of reflux-associated chest pain. Based on our data, it can be inferred that the presence of a large volume of acid refluxate for a longer period of time plays an important role in perceiving a reflux episode as chest pain. The presence of typical reflux symptoms increases the likelihood that reflux is involved in the generation of the chest pain.
REFERENCES


