Towards better understanding of symptoms associated with disordered esophageal function
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DIAGNOSTIC YIELD OF 24-HOUR ESOPHAGEAL MANOMETERY IN NON-CARDIAC CHEST PAIN

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ABSTRACT

Introduction
In the past, ambulatory 24-hour manometry has been shown useful for the evaluation of patients with non-cardiac chest pain (NCCP). With the diagnostic improvements brought by pH-impedance monitoring and high-resolution manometry (HRM), the contribution of ambulatory 24-hour manometry to the diagnosis of esophageal hypertensive disorders has become uncertain. Our aim was to assess the additional diagnostic yield of ambulatory manometry to HRM and ambulatory pH-impedance monitoring in this patient population.

Methods
All patients underwent 24-hour ambulatory pressure-pH-impedance monitoring and HRM. Patients had retrosternal pain as a predominant symptom, and no explanation after cardiologic and digestive endoscopic evaluations. Diagnostic measurements were analyzed by two independent physicians.

Results
Fifty-nine patients met the inclusion criteria. 37.3% of the patients had their symptoms explained by abnormalities on pH-impedance monitoring, and 6.8% by ambulatory manometry. Functional chest pain was diagnosed in 52.5% of the patients. High-resolution manometry, using the Chicago Classification v3.0 criteria alone, did not identify any of the 4 patients with esophageal spasm on ambulatory manometry. However, taking into account other abnormalities, such as simultaneous (rapid) or repetitive contractions, HRM had a sensitivity of 75% and a specificity of 98.2% for the diagnosis of esophageal spasm.

Conclusions
In the work-up of NCCP, ambulatory 24-hour manometry has a low additional diagnostic yield. However, it remains the best technique to identify esophageal spasm as the cause of symptoms. This is particularly useful when an unequivocal diagnosis is needed before treatment.
INTRODUCTION

Non-cardiac chest pain (NCCP) is a common disorder, thought to occur in 13-25% of the population\(^1,2\). It is characterized by episodes of retrosternal chest pain which remain unexplained after a cardiac workup. NCCP is a significant burden to society due to the healthcare seeking attitude and the work absenteeism induced by the symptoms\(^3\). Symptoms are generally related to the esophagus, through visceral hypersensitivity, abnormal cerebral pain processing, altered autonomic activity, gastroesophageal reflux disease (GERD), or esophageal dysmotility, typically hypertensive, spastic, or nonspecific motility disorders\(^1,2,4,5\). The most clearly identified risk factors for NCCP is the presence of GERD\(^2,6,7\).

Upper gastrointestinal endoscopy can demonstrate an esophageal stricture, signs of gastroesophageal reflux or eosinophilic esophagitis as a cause for NCCP. However, functional esophageal testing, including esophageal stationary manometry and pH-impedance monitoring, is usually required in the patient workup. It can identify esophageal motility disorders, non-erosive gastroesophageal reflux disease, or functional chest pain, and provide guidance in the choice of the appropriate treatment\(^8\). Since esophageal spasm may occur randomly during the day, and can therefore be missed during the stationary manometry recording, it is not surprising that ambulatory 24-hour manometry has proved to be more sensitive than conventional stationary manometry\(^9\). Ambulatory manometry has not become widespread however, mainly due to a poor diagnostic yield for motor abnormalities and the difficult interpretation of the findings in terms of clinical relevance\(^1\).

In recent years, major changes in esophageal functional testing have occurred: first, the introduction of reflux detection with impedance monitoring in addition to pH recording, allowing better discrimination of hypersensitive esophagus from functional heartburn or functional chest pain\(^10\); second, the introduction of high-resolution manometry (HRM), and thirdly, novel definitions of hypertensive motility disorders\(^11\). Our aim was to assess the additional yield of ambulatory pressure-pH-impedance monitoring in comparison to stationary HRM alone in patients with non-cardiac chest pain.

METHODS

Subjects
Consecutive patients with retrosternal pain as a main symptom who underwent stationary manometry and combined 24-hour ambulatory pressure-pH-impedance monitoring between 2011 and 2015 were eligible for inclusion. Patients had a preliminary workup including an upper gastrointestinal endoscopy and a cardiologic assessment that did not explain the retrosternal pain. If eosinophilic esophagitis was suspected, further diagnostic testing was performed to rule this out. All electronic
patient records were reviewed in detail for demographic data, medical history and high-resolution manometry and endoscopy reports. Diagnostic measurements were analyzed by two independent physicians, and in the case of disagreement, consensus was made.

The study proposal was submitted to the local institutional review board of the Academic Medical Center in Amsterdam, the Netherlands, and formal ethics evaluation was waived as it was deemed not necessary under Dutch law.

**Stationary high-resolution manometry**

Stationary esophageal HRM studies were performed according to the standardized protocol used in our center, using a solid-state HRM system (Given, Yoqneam, Israel and MMS, Enschede, The Netherlands)\(^\text{12}\). Both solid-state HRM catheters comprised 36 pressure sensors spaced at 1-cm intervals. Prior to the study, participants had fasted for 4 hours. The HRM catheter was placed transnasally and positioned to record from hypopharynx to stomach. Subsequently, participants were placed in a supine position and were asked to perform a series of 10 swallows of 5 mL of water. After the 10 swallows, participants were instructed not to swallow during 30 s, enabling a landmark recording to place the anatomical markers during analysis. Analyses were performed according to a previously described method\(^\text{12}\).

**Ambulatory 24-hour pressure and pH-impedance monitoring**

Proton-pump inhibitor treatment was discontinued 7 days before 24-hour pH-impedance-pressure measurement\(^\text{13}\). Intraesophageal pressure was recorded using an 8 French solid-state manometric catheter with 3 to 4 pressure sensors separated by 5-cm intervals, the most distal of which was positioned in the lower esophagus (ref K8304-00-0075-D, Unisensor, Attikon, Switzerland). The 24-hour pH-impedance measurements were obtained using a combined pH-impedance catheter assembly (Unisensor, Attikon, Switzerland), which was placed such that the pH sensor was positioned at 5 cm from the upper border of the manometrically localized lower esophageal sphincter. Both catheters were introduced via the same nostril and attached to the face. Impedance, pH and pressure signals were stored on a digital datalogger (Ohmega, MMS, Enschede, The Netherlands). A two-minute time window before each symptom was used for symptom analysis\(^\text{14}\).

**Data Analysis**

Esophageal chest pain was defined as midline chest pain or discomfort that is not of burning quality\(^\text{7}\) and had not been diagnosed as due to ischemic heart disease by a physician\(^\text{15}\). A spastic contraction was defined as a high-amplitude contraction (>100mmHg), with a duration of at least 3 seconds (to exclude artifacts such as cough), recorded simultaneously on two or more esophageal pressure channels, typically
with a multipeaked, repetitive configuration. A rapid contraction on high-resolution manometry was defined as a contraction with a contractile front velocity >9 cm/s\(^1\), irrespective of the distal latency value.

The symptom index (SI) was determined for both reflux and abnormal motility and expressed as a percentage. It was calculated as the number of symptom episodes associated with reflux (or dysmotility) divided by the total number of specific symptom episodes, multiplied by 100\(^1\). The cutoff point for a positive correlation between symptom and reflux or dysmotility was 50% (SI positive if \(\geq 50\%\)). The symptom association probability (SAP) was also calculated for both reflux and esophageal dysmotility. The SAP expresses the likelihood that the patients’ symptoms are related to reflux or spasm, and was calculated by dividing 24-hour data into consecutive two-minute segments, with or without reflux and symptom: Fisher’s exact test was used to calculate the probability that the observed distribution could have been brought about by chance\(^1\). By statistical convention, SAP \(\geq 95\%\) is positive. When SI and SAP were discordant, SAP was regarded as the most reliable symptom association score. Hypersensitive esophagus was defined as a normal esophageal acid exposure time (<6% total time with pH < 4) but a positive symptom-reflux association (SI \(\geq 50\%\), SAP \(\geq 95\%\)).

**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). Continuous data were expressed as median and interquartile range (IQR). Patient groups were compared using the Mann–Whitney U-test. Proportions were compared using the chi-squared test. We considered p<0.05 statistically significant.

**RESULTS**

**Patient population**

Fifty-nine patients underwent HRM and ambulatory impedance-pH-pressure monitoring for retrosternal pain as a main indication. Median (IQR) patient age was 59 (51-66) years, and 40.7% were males. Main patient characteristics are presented in Table 1. A cardiac origin was ruled out or deemed unlikely by a cardiologist. An upper endoscopy was performed in 57 (96.6%) patients, and was normal in 48 (81.4%). Esophageal biopsies had been performed in 14 (23.7%) patients, of which two showed signs of Barrett esophagus and the rest were normal. Finally, 14 (23.7%) patients had a significant psychological comorbidity requiring therapeutic intervention.

**Symptom characteristics**

The main symptom leading to the ambulatory manometry was retrosternal pain in all patients, and required conventional analgesics in 12 (20.3%) patients namely
paracetamol or NSAIDS in 5 (8.5%) cases, codeine or tramadol in 5 (8.5%) cases, and morphine in 3 (5.1%) cases. The pain episodes lasted less than 10 minutes in 35%, between 10 and 30 minutes in 22.5%, and over 30 minutes in 42.5% of the patients. 16.7% of patients had symptoms several times per day, and 50.0% had symptoms several times per week. The intensity of the pain episodes varied from mild in 77.6% of the cases, to moderate in 12.2%, and severe in 10.2% of patients. Proton pump inhibitors had been tried in all patients, and 52 (88.1%) were still using this treatment, either at a single (n = 14, 23.7%) or a double dose (n = 38, 64.4%).

In addition to the symptom chest pain, heartburn, regurgitation, dysphagia, nausea or vomiting, belching and weight loss were reported by 9 (15.3%), 15 (25.4%), 14 (23.7%), 2 (3.4%), 4 (6.8%) and 9 (15.3%) patients, respectively.

**Stationary high-resolution manometry**

According to the Chicago classification v3.0\(^{11}\), stationary high-resolution manometry was normal in 35 (59.3%) cases, and showed ineffective esophageal motility in 15 (25.4%) cases and esophagogastric junction outflow obstruction in 9 (15.3%) cases. The median (IQR) Distal Contractile Integral was 1160 mmHg (515-2199 mmHg) and Distal Latency was 6.6 s (5.9-7.5 s). Noticeably, no hypercontractile (Jackhammer) esophagus or distal esophageal spasm was present according to the Chicago Classification v3.0. However, other features suggestive of esophageal spasm in this context were seen in 4 HRM recordings, including 3 otherwise normal HRM studies with repetitive contraction patterns (Figure 1) and 1 with ≥20% rapid contractions. According to the Chicago Classification v3.0, three of the four patients with esophageal spasm diagnosed on 24 hour ambulatory manometry ended up with a diagnosis of “normal esophageal motility” and one with the diagnosis of “ineffective esophageal motility”. The main results of the functional tests for the 4 patients with a diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median age (years)</th>
<th>Female gender (%)</th>
<th>Body mass index (kg/m(^2)) (IQR)</th>
<th>Psychological comorbidity, n (%)</th>
<th>Endoscopic diagnosis, n (%)</th>
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<tbody>
<tr>
<td>Median age (years)</td>
<td>59</td>
<td>35 (59.3)</td>
<td>26.7 (22.2-28.3)</td>
<td>14 (23.7)</td>
<td>57 (96.6)</td>
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<tr>
<td>Female gender (%)</td>
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<td>Body mass index (kg/m(^2)) (IQR)</td>
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Table 1. Baseline characteristics of the patients
of esophageal spasm on 24 hour ambulatory manometry are shown in Table 2. In these patients, HRM showed a median (IQR) integrated resting pressure of 6.1 mmHg (1.6-13.6 mmHg), a median (IQR) distal contractile integral of 3883 mmHg (2494-5214 mmHg), and a median (IQR) distal latency of 5.9 s (4.9-6.5s). Three out of the four patients had repetitive or rapid contractions on HRM.

**Ambulatory 24-hour pressure-pH-impedance monitoring**

Eighteen (30.5%) patients did not experience a single chest pain episode during the 24-hour recording. As shown in Figure 2, ambulatory 24-hour pH-impedance monitoring documented gastroesophageal reflux disease in 17 (28.8%) patients and hypersensitive esophagus in 5 (8.5%). Four patients had a final diagnosis of (distal) esophageal spasm based on 24-hour manometry (Figure 3): they were two men and two women, aged 60 to 76 years, reporting a median (IQR) of 4 (2-8) chest pain episodes during the monitoring, with a median (IQR) SAP for spasms of 98.9% (97.4-99.6%), a median (IQR) total acid exposure time of 5.1% (0.8-9.4%), and a median (IQR)

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**Table 2.** Main results of stationary high resolution manometry, ambulatory 24h pH-impedance and manometry monitoring for the 4 patients with a diagnosis of esophageal spasms (positive 24h measurement).

<table>
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<th>High resolution manometry</th>
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<td>Integrated resting pressure (mmHg) *</td>
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<td>Distal contractile integral (mmHg) *</td>
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<tr>
<td>Distal latency (s) *</td>
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<tr>
<td>Ineffective contractions (%) *</td>
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<tr>
<td>Presence of repetitive contraction patterns or rapid contractions, n (%)</td>
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<td>Repetitive</td>
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<td>Rapid</td>
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**Final diagnosis on high-resolution manometry, n (%)**

| Normal esophageal motility | 3 (75) |
| Ineffective esophageal motility | 1 (25) |

**24-h manometry with pH-impedance recording**

| Reflux symptoms (heartburn or regurgitation) during recording* | 7 (5-10) |
| Chest pain episodes during monitoring* | 4 (2-8) |
| Total acid exposure time (%)* | 5.1 (0.8-9.4) |
| Number of reflux episodes* | 20 (5-32) |
| SI for reflux (%)* | 12.5 (0-31.2) |
| SAP for reflux (%)* | 43.7 (0-96.1) |
| SI for spasms (%)* | 63.4 (48.3-91.7) |
| SAP for spasms (%)* | 98.9 (97.4-99.6) |

*Data are expressed as median (IQR). ** According to the Chicago Classification v3.0. SI: symptom index; SAP: symptom analysis probability
SAP for reflux of 43.7% (0-96.1%). More detailed characteristics of the esophageal functional tests in these patients are reported in Table 2. Spastic contractions were only seen in patients with a final diagnosis of esophageal spasms. In one patient however, simultaneous contractions below 100 mmHg of amplitude were seen, yet due to the low amplitude this was not considered to be relevant.

**Figure 1.** Stationary high-resolution manometry showing repetitive contractions patterns following each swallow.

**Figure 2.** Final diagnosis after high-resolution manometry (HRM) and 24-hour ambulatory pH-impedance-pressure monitoring. 24-hour ambulatory manometry was used to make the diagnosis of esophageal spasm.
Diagnostic yield of each investigation
Taking ambulatory 24-hour manometry as the gold standard, 4 patients had convincing evidence that esophageal spasm explained their symptoms.

HRM, when taking into account the presence of repetitive contraction features or ≥20% rapid ("simultaneous") contractions, identified three out of four of the patients with esophageal spasm, resulting in a sensitivity of 75% and a specificity of 98.2% for the diagnosis of esophageal spasm in our NCCP patient group. HRM also

Figure 3. 24-hour pressure-pH-impedance monitoring. A and B: simultaneous contractions of high (>100 mmHg) amplitude.
misclassified one patient, raising suspicion of esophageal spasm in one patient with repetitive contractions, while 24-hour manometry was negative. Of the eight patients taking opiate derivates, none had signs of spasm on either HRM or 24 hour ambulatory manometry.

pH-impedance monitoring allowed to link the symptoms to gastroesophageal reflux disease or hypersensitive esophagus in 22 (37.3%) patients. Finally, 31 (52.5%) patients had a final diagnosis of functional chest pain and were managed either expectatively, or with antidepressants. Among the 14 patients with psychological comorbidity, functional chest pain was diagnosed in 7 (50%) as compared to 21 (46.7%) in the other study patients (p=0.5).

**DISCUSSION**

To our knowledge, this is the first study in patients with NCCP in which a functional esophageal testing protocol was used that combined stationary high-resolution manometry and ambulatory 24-hour pressure-pH-impedance monitoring. In this referral center experience, the isolated diagnostic yield of ambulatory 24-hour manometry for esophageal spasm was only 6.8%. High-resolution manometry, using the Chicago v3.0 criteria alone, did not identify any of these patients. However, when “suggestive” abnormalities, such as rapid (simultaneous) or repetitive contractions, were taken into account, HRM detected four patients, of which three were found to have spastic contractions that were followed by pain during ambulatory manometry.

In 1986, Janssens et al. were the first to publish on the application of ambulatory esophageal manometry in NCCP. In their study in 60 patients, they demonstrated that ambulatory manometry allowed to link the symptoms to an esophageal abnormality in 13.3 % of the patients. Although the contribution of ambulatory manometry has been questioned, either because of a poor diagnostic yield or due to a difficult interpretation of the abnormal esophageal contractions recorded, most of the subsequent studies positioned ambulatory manometry as a gold standard for the diagnosis of esophageal spasm in the setting of NCCP. Normative values were published.

In order to avoid ambulatory 24-hour manometry, many efforts have been made to diagnose esophageal spasm using stationary manometry. In a large study including 910 patients with chest pain, it was found that nutcracker esophagus (high-amplitude contractions) was the most common manometric finding in NCCP patients, observed in 13.5% of the study group. In another study including 140 patients with NCCP, it was observed that 30% of the patients had an abnormal esophageal manometry, with the following distribution: 61% of the patients had a hypotensive lower esophageal sphincter, 10% a nutcracker esophagus, 10% a hypertensive lower esophageal sphincter, 2% diffuse esophageal spasms, 5% an ineffective esophageal peristalsis, 2% achalasia, and the remaining 10% of the patients had nonspecific esophageal motility disorders.
“Multipeaked” or repetitive contractions have been proposed as a marker on stationary manometry for esophageal hypertensive disorders\textsuperscript{30-32}. Roman et al. recently demonstrated that repetitive contraction features were associated with hypercontractile esophagus in 82\% of cases\textsuperscript{33}. Our results support this conclusion, since half of the patients with esophageal spasm had repetitive contractions on HRM.

Rapid or simultaneous contractions, as identified by a high contractile front velocity (above 8 or 9 cm/s) was proposed as a diagnostic marker of distal esophageal spasm on conventional manometry\textsuperscript{32,34} and later on HRM\textsuperscript{16}. However, it was later demonstrated that a rapid contractile front velocity lacked specificity, and was associated with a great variety of manometric diagnoses, among which only 7\% hypertensive peristalsis\textsuperscript{16}. Therefore, the third version of the Chicago classification of esophageal motility disorders defines distal esophageal spasm exclusively by shortened contractile latency (distal latency < 4.5s in at least 20\% of the swallows) rather than by an increased contractile front velocity. Furthermore, specific contraction patterns, such as repetitive contractions, are not taken into account\textsuperscript{11}. Our data suggest that abnormalities such as rapid or repetitive contractions on HRM are highly suggestive of esophageal spasm, and should be resurrected as diagnostic features. This conclusion is supported by a recent publication from our group that demonstrated that in patients with rapid (simultaneous) contractions, symptoms, radiographic findings and manometric findings were not different from those found in patients with shortened distal latency\textsuperscript{35}.

However, defining esophageal spasm only as a manometric abnormality, without any temporal relationship with the symptoms, might be insufficient. Of the four patients with suggestive HRM, three were ultimately diagnosed with esophageal spasm, based on the symptom association analysis performed on data from the ambulatory manometry. Even if current management of esophageal spasm usually is conservative, with either expectative management or - poorly effective - medical therapy, more aggressive treatment options, such as peroral endoscopic myotomy, are emerging\textsuperscript{36}. It can be argued that a definitive diagnosis of esophageal spasm based on ambulatory 24-hour manometry is needed before invasive and irreversible therapy is considered.

In a recent literature review, Coss-Adame et al. showed that, in patients with NCCP, PPIs, theophylline, antidepressants and cognitive behavioral therapy were more effective than calcium blockers and nitrates, or even botulinum toxin and esophageal myotomy\textsuperscript{8}. Clearly, this finding reflects the fact that the spectrum of NCCP mainly comprises patients with functional chest pain and GERD. Our figures in terms of final etiology for NCCP are in accordance with most publications in the field, with a GERD prevalence of 24-45\%, and esophageal dysmotility in 4.5-17.3\%\textsuperscript{1,9,26,37-40}.

In 44 patients with NCCP, Breumelhof et al., using ambulatory pH and pressure monitoring, found motor abnormalities accounting for symptoms in up to 13.6\% of their patients\textsuperscript{23}. These figures, comparable to those of Janssens et al.\textsuperscript{19}, can be explained by the use of less stringent criteria for a positive relationship.
Besides its relatively large patient sample, one of the main strengths of our study is that we are the first group to research the benefit of ambulatory manometry in NCCP patients who have undergone HRM. Based on the literature, we used ambulatory manometry as the gold standard to diagnose esophageal hypertensive disorders. However, this “gold standard” might still be suboptimal, since esophageal spasm and symptoms do not occur several times a day in most patients\(^2\). Similarly, in our study, 30.5% of the patients did not experience a single chest pain episode during the 24-hour recording.

In conclusion, ambulatory 24-hour manometry resulted in a positive diagnosis of esophageal spasm in only 6.8% of NCCP patients in our study. High-resolution manometry identified three fourths of these patients through other contraction patterns such as high propagation velocity or repetitive features, which are not considered abnormal in the latest Chicago Classification. Despite the contribution of high-resolution manometry, ambulatory 24-hour manometry remains the best available method to identify esophageal dysmotility as the cause of the symptoms, as it allows the assessment of the temporal relationship between reported symptoms and spastic contractions. Finally, our study confirmed that pH-impedance monitoring is the most useful investigation in non-cardiac chest pain patients, demonstrating a reflux-related origin of the symptoms in more than a third of the patients.
REFERENCES


