Towards better understanding of symptoms associated with disordered esophageal function
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SUBTLE LES RELAXATION ABNORMALITIES IN PATIENTS WITH UNEXPLAINED ESOPHAGEAL DYSPHAGIA

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ABSTRACT

Background
Esophageal dysphagia is a relatively common symptom. We aimed to evaluate whether subtle, presently not acknowledged forms of dysfunction of the lower esophageal sphincter (LES), could explain dysphagia in a subset of patients with normal findings at high-resolution manometry according to the Chicago classification v3.0.

Methods
We used high-resolution manometry to compare LES relaxation characteristics in 97 patients with unexplained dysphagia with those in 44 healthy subjects. In addition, normative values for time to LES relaxation and completeness of LES relaxation were calculated. Patients with delayed or incomplete LES relaxation were compared with patients with normal relaxation.

Results
Dysphagia patients had a higher nadir LES pressure ($p=0.001$) and a longer time to LES relaxation ($p=0.012$) than healthy subjects. Based on the findings in healthy subjects, normal values of LES relaxation were defined as: $\geq50\%$ of swallows with normal LES relaxation time (<5s) and $\leq20\%$ of swallows with incomplete LES relaxation (not reaching a value below 10 mmHg). Dysphagia patients had significantly more often $>50\%$ swallows with delayed and/or incomplete LES relaxation than healthy controls (25\% versus 4.5\%; $p=0.004$). Dysphagia patients with $>50\%$ delayed and/or incomplete LES relaxation had a significantly higher LES resting pressure ($p<0.001$) and a significantly higher intrabolus pressure ($p<0.001$) than dysphagia patients who did not fulfill the criteria.

Conclusions
Subtle LES relaxation abnormalities, such as a delayed relaxation of the LES and/or incomplete LES relaxation, could be a cause of dysphagia in approximately one quarter of the patients with otherwise unexplained esophageal dysphagia.
INTRODUCTION

Esophageal dysphagia, defined as a sensation of difficult passage of solids or liquids through the esophagus\(^1\), is a relatively common symptom. Up to 16% of healthy individuals have a history of dysphagia at some point in their life\(^2\). Newly developed dysphagia is considered to be an alarm symptom which warrants further evaluation as it might be related to grave esophageal pathology such as esophageal carcinoma. However, many other etiologies exist, which are traditionally split up into obstructive and non-obstructive causes. This nomenclature is somewhat confusing since not only structural obstruction but also disordered motor function at the level of the esophagogastric junction (EGJ) or in the distal esophagus can have an obstructive effect. These include motility disorders such as achalasia, diffuse esophageal spasm, jackhammer esophagus and esophagogastric junction outflow obstruction\(^1\). In the absence of structural, mucosal, or motor abnormalities to explain the symptom, a diagnosis of functional dysphagia is made\(^3\).

The relaxation of the lower esophageal sphincter (LES) is important for a food bolus to pass into the stomach. Many studies have used conventional manometry to evaluate esophageal contractility and LES relaxation. In these studies, many different criteria were used to determine whether the LES relaxation was incomplete. In 1988, Castell et al.\(^4\) evaluated different pressure parameters of the LES including the resting sphincter pressure, the percent of LES relaxation, the duration of LES relaxation, the residual LES pressure during relaxation and the area of relaxation. In their study, the residual pressure at the nadir of LES relaxation was found to be the most important parameter for LES relaxation. Later, in the Spechler and Castell classification of esophageal motility abnormalities for conventional manometry, completeness of LES relaxation was also determined by the residual LES pressure\(^5\).

With the advent of high-resolution manometry (HRM) a new objective measurement of the EGJ relaxation was introduced, namely the integrated relaxation pressure (IRP)\(^6,7\). An IRP measured over 4 seconds and a cut-off value of 15 mmHg were found to provide optimal separation between patients with and without achalasia\(^7\). In the Chicago classification of esophageal motility disorders, the IRP is pivotal in diagnosing achalasia and EGJ outflow obstruction\(^8\). However, this does not exclude the possibility that subtler forms of dysfunction of the EGJ exist, and, consequently, that some patients with unexplained dysphagia are erroneously diagnosed with functional dysphagia. We hypothesized that in a proportion of the patients with unexplained dysphagia that do not meet Chicago criteria for a motility disorder, other, more subtle, motility abnormalities, quantified with HRM, can explain the symptoms. In this study, we aimed, firstly, to evaluate novel HRM-derived metrics of LES relaxation in healthy volunteers, and, secondly, to evaluate whether the use of these metrics allows identification of a subset of patients with unexplained non-obstructive esophageal dysphagia according to the Chicago classification v3.0\(^9\) in whom the dysphagia might be related to subtle abnormalities of LES relaxation.
METHODS

Patients
We conducted an observational study comparing patients with unexplained non-obstructive esophageal dysphagia to healthy subjects. Unexplained non-obstructive esophageal dysphagia was defined as being normal on the Chicago Classification 3.0, including an IRP <15 mmHg and normal peristalsis. We aimed to determine whether incomplete or delayed LES relaxation in patients not meeting the Chicago criteria for EGJ outflow obstruction could explain the dysphagia in a subset of these patients.

We included 97 patients (62 male, age 16 – 74) with unexplained esophageal dysphagia. All these patients had dysphagia as a main symptom, had no abnormalities on upper gastrointestinal endoscopy or another explanation for their symptoms and had a normal high-resolution manometry based on Chicago classification version 3.0⁸. In addition, we included 44 healthy subjects (30 male, age 18 – 64 years). All healthy subjects were symptom-free, did not use regular medication and never had surgery of the upper gastrointestinal tract. They all gave written informed consent. 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.

Esophageal high-resolution manometry
All participants underwent a stationary high-resolution manometry using a solid-state HRM catheter with 36 pressure sensors (Given Imaging, Los Angeles, CA, USA). The manometry catheter was placed transnasally after a 4-hour fasting period and the participant was in the supine position during the measurement. The protocol included ten 5-mL water swallows and a 30-s period without swallowing, allowing a landmark recording to place the anatomical markers during analysis. Computer analyses were performed with appropriate software (Given Imaging, Los Angeles, CA, USA).

Data analysis
During analysis of the manometric recordings, the investigators (TH and FvH) were blinded to the identity of the subject and thus for the group (dysphagic or control). In the HRM recordings, for each of the ten water swallows, the following measurements were made: intrabolus pressure (IBP), LES resting pressure during relaxation of the upper esophageal sphincter (UES), nadir LES pressure and percentage LES relaxation ((resting LES pressure – nadir LES pressure) / resting LES pressure) x 100)).

In accordance with established conventional manometric criteria, LES relaxation was considered to be incomplete if an LES pressure < 10 mmHg was not reached⁵. In all participants we calculated the number of swallows with incomplete LES relaxation.
The time to LES relaxation was defined as the time interval between the onset of UES relaxation and the moment LES pressure fell to < 10 mmHg. Time to LES relaxation was considered to be prolonged when it was above the 95th percentile of time to relaxation in healthy subjects. All pressures related to LES measurements were measured relative to the intragastric pressure.

**Statistical analyses**

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY, USA). Continuous variables were described as median and interquartile range (IQR). Differences between groups were tested with a Mann-Whitney U test for numerical data. Relationships between parameters were expressed using the Spearman’s Rank correlation. Normative values for time to LES relaxation and completeness of LES relaxation were based on the 95th percentile of the parameters in the healthy subjects. Finally, we compared patients with delayed or incomplete LES relaxation to patients with normal relaxation. We considered p<0.05 statistically significant.

**RESULTS**

LES relaxation characteristics in 97 patients with unexplained esophageal dysphagia were compared to those recorded in 44 healthy subjects. Table 1 shows the manometric characteristics of the patients and controls. The nadir LES pressure was significantly higher in dysphagia patients (6.1 mmHg (4.6 - 7.9)) than in healthy subjects (4.3 mmHg (2.5 - 5.9)); p = 0.001. In accordance, the percentage LES relaxation was lower in dysphagia patients (71%) than in healthy subjects (78%); p = 0.036. The intrabolus pressure was comparable between both groups (table 1).

Dysphagia patients had a significantly longer time to LES relaxation (3.7 s (2.2 - 4.7) than healthy subjects (2.7 s (0.5 - 4.1); p = 0.012. In healthy subjects, the 95th percentile of time to LES relaxation was 5 s. In addition, the 95th percentile

<table>
<thead>
<tr>
<th>Table 1. Manometry parameters of patients and controls</th>
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<tbody>
<tr>
<td><strong>Healthy subjects</strong></td>
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<tr>
<td><strong>N=44</strong></td>
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<tr>
<td>Median intrabolus pressure (mmHg)</td>
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<tr>
<td>Resting LES pressure (mmHg)</td>
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<td>Nadir LES pressure (mmHg)</td>
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<tr>
<td>Percentage LES relaxation</td>
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<tr>
<td>Time to LES relaxation (s)</td>
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Median (IQR). Mann-Whitney U test
for the percentage of swallows associated with a time to LES relaxation > 5 s was 50% and the 95th percentile for swallows with incomplete LES relaxation (LES pressure not falling below 10 mmHg) was 20%. When evaluating the combination of both delayed and/or incomplete LES relaxation, the 95th percentile was 5 swallows (50%).

In table 2, we present the number and percentage of dysphagia patients with an elevated number (above the 95th percentile) of swallows with delayed LES relaxation, incomplete LES relaxation and a combination of both. Significantly more dysphagia patients (19%) had >20% swallows with incomplete LES relaxation, when compared to healthy subjects (2%); \( p = 0.007 \). Also, dysphagia patients (25%) had significantly more often > 50% delayed and/or incomplete LES relaxation than healthy controls (4.5%); \( p = 0.004 \).

**Comparing dysphagia patients with and without LES relaxation abnormalities**

Finally, we compared dysphagia patients with LES relaxation abnormalities to dysphagia patients with normal LES relaxation (table 3). Dysphagia patients who fulfilled the criteria of > 50% delayed and/or incomplete LES relaxation had a significantly higher LES resting pressure (30.6 (24.6 – 37.2)) than dysphagia patients who did not fulfill the criteria (18.6 (14.5 – 24.6)); \( p < 0.001 \). They also had a significantly higher median IBP (5.3 versus 1.8; \( p < 0.001 \)) than dysphagia patients who did not fulfill the criteria (figure 1). In figure 2 an example of a delayed LES relaxation with elevated intrabolus pressure is shown.

There was no correlation between age and LES relaxation parameters, suggesting that age has no influence on our findings on LES relaxation abnormalities. Spearman correlation between age and nadir LES pressure (\( p = 0.738 \)), percentage LES relaxation (\( p = 0.105 \)), intrabolus pressure (\( p = 0.447 \)), time to LES relaxation (\( p = 0.912 \)) and number of swallows with incomplete relaxation (\( p = 0.156 \)), were not statistically significant.

<table>
<thead>
<tr>
<th>Table 2. Prevalence of subtle LES relaxation abnormalities in patients with dysphagia</th>
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<tbody>
<tr>
<td><strong>Dysphagia patients N=97</strong></td>
</tr>
<tr>
<td>&gt; 50% delayed LES relaxations</td>
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<tr>
<td>&gt; 20% incomplete LES relaxations</td>
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<tr>
<td>&gt; 50% delayed and/or incomplete LES relaxations</td>
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**DISCUSSION**

In this study, we demonstrate that subtle LES relaxation abnormalities could explain dysphagia in a subset of patients with unexplained non-obstructive esophageal
Table 3. Comparison of dysphagia patients with and without LES relaxation abnormalities

<table>
<thead>
<tr>
<th></th>
<th>Normal LES relaxation</th>
<th>&gt; 50% delayed and/or incomplete LES relaxations</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=73</td>
<td>18.6 (14.5 - 24.6)</td>
<td>30.6 (24.6 - 37.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IBP median</td>
<td>1.8 (0.1 - 3.95)</td>
<td>5.3 (3.6 - 6.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Percentage relaxation</td>
<td>71 % (61 - 80 %)</td>
<td>70 % (63 - 77 %)</td>
<td>0.748</td>
</tr>
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</table>

Median (IQR). Mann-Whitney U test

Figure 1. Intrabolus pressures of subgroups of patients with non-obstructive dysphagia. Intrabolus pressures were significantly higher in patients with >50% delayed LES relaxations (p=0.03), in patients with >20% incomplete LES relaxations (p<0.001) and in patients with > 50% delayed and/or incomplete LES relaxations (p<0.001), compared to patients without relaxation abnormalities.

dysphagia according to the Chicago classification v3.0. Most current guidelines recommend that, after exclusion of structural lesions as a cause of dysphagia, esophageal manometry is performed to exclude motor disorders which could explain the symptom. In the Chicago classification, these include achalasia, EGJ outflow obstruction, absent contractility, jackhammer esophagus and distal esophageal spasm. In the case of achalasia and EGJ outflow obstruction, the IRP is used to determine whether the LES relaxation can be considered as normal. The IRP is a metric in which the mean of the 4 seconds of maximal deglutitive relaxation in the 10-second window beginning at UES relaxation is calculated. If this value is below 15 mmHg, then LES relaxation is considered to be normal. The IRP has proven to be of great importance in diagnosing patients with achalasia. However, it has also been shown that the IRP is not perfect in identification of achalasia patients. Furthermore, the contributing stretches for the 4 seconds used in the calculation of the IRP can be non-contiguous.
Therefore, the IRP can be normal even if LES pressure remains high at the start of the swallow.

In our study, we found that patients with unexplained non-obstructive esophageal dysphagia had a significantly longer interval between swallow and LES relaxation than healthy controls (2.7 vs 3.7 seconds, p<0.012). It is known that, in the upright position, the leading edge of a liquid bolus is transported by gravity and can enter the stomach within 6 seconds after swallowing, prior to the arrival of the peristaltic contraction. As a result, it is conceivable that a delay in the opening of the LES could result in the perception of incomplete passage, even if the LES does relax sufficiently at a later moment. Moreover, it is important to bear in mind that there is a difference between relaxation and opening of the LES, and that manometry only measures the relaxation-related pressure fall and not the opening of the LES. When the intraluminal diameter of the LES is greater than the diameter of the catheter, the catheter will record complete manometric relaxation, even though sphincter opening might not be sufficient for a bolus to pass unhindered. We found a significantly higher nadir LES pressure (6.1 mmHg vs 4.3 mmHg, p=0.001) and a significantly lower percentage relaxation (71% vs 78%, p=0.036) in patients with dysphagia compared to the healthy subjects.
could therefore be that in a subset of the dysphagia patients the threshold necessary for unhindered passage to the stomach is not reached, resulting in dysphagia.

To our knowledge, this study is the first that considered a delay in opening of the LES as a potential cause of dysphagia. In our study, we used a threshold of 10 mmHg for complete LES relaxation. This value is in line with previous, conventional, manometric studies⁵. We observed that in healthy controls the time interval between swallow and LES relaxation, defined as the time from UES relaxation until the moment that LES pressure falls to a value below 10 mmHg, can last up to 5 seconds. Moreover, we found that a delayed and/or incomplete relaxation of the LES can be found in up to 5 out of the 10 wet swallows in healthy subjects. In the analysis of manometric studies in 97 patients with unexplained non-obstructive esophageal dysphagia, we found that 24 patients (25%) had >50% of swallows with a delayed and/or incomplete LES relaxation. These patients had a significantly higher resting LES pressure. Intuitively, it is understandable that when the resting LES pressure is higher, a low LES pressure is less likely to be reached during relaxation. More importantly, we found that patients with >50% delayed LES relaxations, patients with >20% incomplete LES relaxations, and patients with >50% delayed and/or incomplete LES relaxations had significantly higher IBP when compared to patients with normal LES relaxation. This supports the notion that during suboptimal LES relaxations the flow across the EGJ might be hindered.

Our findings may be of clinical relevance because currently patients not meeting the Chicago criteria for a motility disorder are labeled as having functional dysphagia, and, consequently, treated as such with perception modulators³. Possibly, these patients would respond better to other treatment options. It has been described that empiric bougie dilation benefits 68-85% of patients with intermittent food dysphagia without an identifiable source¹¹,¹². It would therefore be interesting to study the effect of bougie dilation in patients with subtle disorders of LES relaxation.

In conclusion, subtle LES relaxation abnormalities, such as a delayed relaxation of the LES and/or failure of LES relaxation to reach a threshold of 10 mmHg, could be a cause of dysphagia in approximately one quarter of the patients with non-obstructive esophageal dysphagia and absence of EGJ outflow obstruction according to the current Chicago classification (v3.0).
REFERENCES


