Reflux disease and achalasia: Failure of the gatekeeper

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Chapter 3

High Resolution Esophageal Pressure Topography is superior to conventional sleeve manometry for the detection of Transient Lower Esophageal Sphincter Relaxations associated with a reflux event.

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ABSTRACT

Background and aims: 
Transient lower esophageal sphincter relaxations (TLESRs) are the main mechanism underlying gastroesophageal reflux and are detected during manometric studies using well defined criteria. Recently, high resolution esophageal pressure topography (HREPT) has been introduced and is now considered the new standard to study esophageal and lower esophageal sphincter (LES) function. In the present study we performed a head-to-head comparison between HREPT and conventional sleeve manometry for the detection of TLESRs.

Methods: 
A setup with two synchronized MMS-solar systems was used. A solid state HREPT catheter, a water perfused sleeve catheter and a multi intraluminal impedance pH (MII-pH) catheter were introduced in ten healthy volunteers (M6F4, age 19-56). Subjects were studied 0.5hr before and 3hrs after ingestion of a standardized meal. Tracings were blinded and analyzed by the three authors according to the TLESR criteria.

Results: 
In the HREPT mode 157 TLESRs were scored, versus 143 during sleeve manometry (P=0.08). 123 TLESRs were scored by both techniques. Of all TLESRs (177), 138 were associated with reflux (78%). HREPT detected significantly more TLESRs associated with a reflux event (132 vs 119, P=0.015) resulting in a sensitivity for detection of TLESRs with reflux of 96% compared to 86% respectively. Analysis of the discordant TLESRs associated with reflux showed that TLESRs were missed by sleeve manometry due to low basal LES pressure (N=5), unstable pharyngeal signal (N=4) and residual sleeve pressure > 2mmHg (N=10).

Conclusion: 
HREPT is superior to sleeve manometry for the detection of TLESRs associated with reflux. However, rigid HREPT criteria are awaited.
INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition characterized by reflux of gastric contents causing troublesome symptoms and/or complications. It is widely accepted that transient lower esophageal sphincter relaxations (TLESRs) are the main mechanism underlying the occurrence of gastroesophageal reflux, both in patients with GERD and healthy subjects. TLESRs occur as frequent in healthy volunteers as in patients with GERD. However, in patients TLESRs are more often accompanied by acid reflux, presumably at least partly due to the position of the gastric acid pocket. A TLESR is a vago-vagal reflex triggered by various stimuli, of which gastric distention is probably the most important. After activation, the specific motor pattern underlying TLESRs is triggered, causing a relaxation of the lower esophageal sphincter (LES), esophageal shortening, and inhibition of the crural diaphragm. New pharmacological agents inhibiting TLESRs are currently evaluated in clinical trials. These reflux inhibitors may prove a more physiological treatment for GERD, or more likely can be used as an add-on therapy in combination with proton pump inhibitors.

Objective criteria for detection of TLESRs were described in a keystone article of Holloway et al. Criteria were defined by distinguishing LES relaxations during dry and water swallows from LES relaxations with acid reflux, which were detected by pH-metry. The criteria were designed for water perfused manometry with a sleeve sensor and have been widely used since then. Until recently sleeve manometry was considered the gold standard to detect TLESRs. As a sleeve sensor records the highest pressure along a 6 cm membrane covering a perfused chamber positioned at the level of the LES, reliable recording of sphincter pressure even in case of axial movement during peristalsis, TLESRs or respiration is guaranteed. However, the sensitivity of the sleeve sensor to detect TLESRs has been questioned. In a review by Dent, it was hypothesized that the influence of TLESRs as the mechanism for reflux episodes in patients with GERD is probably underestimated in actual literature. Especially during periods of low LES pressure and during periods of frequent swallowing, TLESRs can easily be missed when criteria are strictly applied. Furthermore, the inter- and intra observer variability for sleeve manometry are only reasonable, and depend on the quality of the tracing.

The development of high resolution esophageal pressure topography (HREPT) has improved our insight in esophageal motility. HREPT uses closely spaced pressure sensors, spaced 1 cm apart, spanning from the pharynx to the gastric lumen, incorporating both esophageal sphincters. The higher spatial resolution of HREPT provides a better understanding of the complex functional anatomy of the esophageal sphincters and peristalsis. Furthermore, the combination of the increased resolution and the isocontour or Clouse plot, a spatiotemporal plot in which a colour represents a pressure, warrants a completely different view of esophageal motility, and simplifies...
the analysis for untrained physicians. In clinical practice it has been shown that HREPT increases diagnostic yield in patients with dysphagia and achalasia, and is therefore considered the new standard to study esophageal motility. HREPT has already demonstrated its value in the complex motor event of TLESRs by showing the esophageal shortening preceding the opening of the LES.

Bredenoord et al. showed that closely spaced water perfused side holes at the level of the LES were as accurate in the detection of TLESRs as a sleeve sensor. However, to what extent the technique using the isocontour plot mode is superior to depict TLESRs remains to be studied. Therefore, the aim of this study is to compare HREPT with sleeve manometry for the detection of TLESRs.

MATERIALS AND METHODS

Subjects
Studies were performed in 10 healthy volunteers (median age 23 (range 19-56), 6 males). All subjects were free of any gastrointestinal symptoms; none had a history of gastrointestinal surgery or took any medication known to influence gastrointestinal motility at time of the study. Each subject gave written informed consent to participate in the study, which was approved by the Medical Ethical Committee of the Academic Medical Center.

Study Protocol
All studies were performed after an overnight fast. Either the HREPT catheter or the sleeve manometry catheter was inserted first through a topically anaesthetized nostril. The HREPT catheter was placed with the most distal 5 sensors positioned in the stomach. The sleeve catheter was placed with the sleeve straddling the LES. To exclude interference with LES function manometry catheters were tested separately first before insertion of the other manometry catheter through the other nostril. No interference between the two catheters was seen regarding the nadir pressure, relaxation rate and relaxation time of the LES. (table 1) Subsequently, the MII-pH catheter was placed. TLESRs were studied during a basal period of 30min and 3-hour TLESR-recordings after a standardized meal, consisting of two pancakes with jam and 200 mL of orange juice (510 Kcal). During the study subjects were in a semi-recumbent position.

Recording methods
Two separate MMS GI Solar systems (MMS, Enschede, The Netherlands) were used in a parallel setup, after synchronisation for time. Sleeve manometry was performed using a 10-lumen silicone rubber assembly (Dentsleeve International Ltd, Mississauga, ON, Canada) with a 6-cm long reversed perfused sleeve sensor incorporated at its distal end to monitor LES pressure. Side
holes monitored pressure in the stomach (3 cm below the distal margin of the sleeve), just at the proximal margin of the sleeve and at 4, 9, 14, 19 and 24 cm above the sleeve. Four pharyngeal side holes were available to monitor swallows, of which one was selected for this purpose. The side holes and the sleeve were perfused with degassed distilled water at 0.2 mL/min, using a pneumohydraulic capillary perfusion pump (Dentsleeve Pty, Belair, South Australia) and hydraulic flow restrictors (Dentsleeve International Ltd). HREPT recordings were performed using a solid state high-resolution catheter (Unisensor, Attikon, Switzerland) with 36 solid state pressure transducers spaced 1 cm apart. Pressure sensors were zeroed before insertion, and the sample rate was 50 Hz. A combined MII-pH catheter (VersaFlex, Alpine Biomed, Skovlunde, Denmark), containing 6 pairs of impedance electrodes and 1 antimony pH sensor with internal reference was used. The design of the catheter allowed impedance recordings at 3, 5, 7, 9, 15 and 17 cm above the upper border of the LES and pH recording at 5 cm above the LES. Impedance and pH data were sampled at a frequency of 50 and 2 Hz, respectively. The pH electrode was calibrated using buffers solutions of pH 4.0 and pH 7.0 (Medtronic A/S, Skovlunde, Denmark) before each study.

**Data analysis**

All investigators (WR, GB, DH) analyzed manometry tracings separately after blinding. A TLESR was scored when there was agreement between at least two out of the three investigators. TLESRs were evaluated according to previously published criteria:

1. absence of swallowing for 4 s before to 2 s after the onset of LES relaxation,
2. relaxation rate of ≥ 1 mmHg/s,
3. time from onset to complete relaxation of ≤ 10 s, and
4. nadir pressure of ≤ 2 mmHg.

LES relaxations associated with a swallow and fulfilling the above mentioned criteria 2, 3 and 4 that lasted more than 10 s were included as TLESR. According to the modified criteria described by Holloway et al. inhibition of the crural diaphragm and a prominent after contraction were also taken into account.

All criteria for sleeve manometry were also applied to HREPT. For determination of nadir pressure and relaxation rate the vSleeve feature of MMS software was used. This part of the software integrates all pressure values to one tracing mimicking the function of the sleeve, after visual location of the upper and lower limit of the LES. Esophageal shortening is attributable to longitudinal muscle contraction, and can be seen during peristalsis, TLESRs and esophageal spasm. HREPT can be used to visualize esophageal shortening as was shown in previous studies. Esophageal shortening is defined as the axial movement of the upper border of the LES, which can be determined during a TLESR.

A reflux event was defined as either pure liquid, pure gas or a mixture of liquid and gas detected by impedance. Liquid reflux was defined as a fall in impedance of ≥ 40 % of baseline impedance starting at the most distal segment and propagating retrograde to at least the next measuring segment. Pure gas reflux was defined as a rapid (>3000 W/s) rise in impedance, occurring simultaneously in
at least two impedance sites, in the absence of swallowing. Mixed reflux was defined as gas reflux occurring during or immediately before liquid reflux. A reflux episode as recorded by impedance was classified as acid reflux if a pH fall from above to below 4 occurred.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software. Parametric data are presented as mean ± SEM and non-parametric data as median (interquartile range). For statistical analysis, McNemar test was used for paired analysis of dichotomous variables, and Fisher’s exact was used for dichotomous variables with cells < 5. Paired t-test was used for paired data, and student’s t-test for unpaired data. Spearman’s Rho was used for correlations. Inter-observer agreement was calculated by using the mean of percentages of agreement of two authors. P-value < 0.05 was considered as statistically significant.

RESULTS

TLESRs

A total of 177 TLESRs was detected by either recording method, of which 122 were detected by both methods. HREPT detected more TLESRS compared to sleeve manometry, although this did not reach statistical significance (156 vs 143 P = 0.10). Median number of TLESRs per HV was 13.5 (10 – 20.5) using HREPT, and 12.5 (8.5-20.5) using sleeve manometry. The number of TLESRs in HREPT per healthy volunteer correlates well with the number of TLESRs in sleeve manometry (r = 0.88 P<0.001). Nadir pressure during TLESRs is lower using sleeve manometry compared to HREPT (mean 0.1 ± 0.1 mmHg vs 0.6 ± 0.15 mmHg P<0.01)(Table1). TLESR duration is equal in HREPT and sleeve manometry (18.5 ± 0.6 s vs 17.3 ± 0.6 s, P=0.06). (Table 1) Mean percentage of agreement for sleeve manometry was 81% (78-83%) and 80% (75-86%) for HREPT.

<table>
<thead>
<tr>
<th>Wet swallows separate catheters</th>
<th>Relaxation rate (mmHg/s)</th>
<th>Relaxation time (s)</th>
<th>Esophageal Shortening (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HREPT</td>
<td>2.1 ± 0.38</td>
<td>4.7 ± 0.52</td>
<td>6.6 ± 0.31</td>
</tr>
<tr>
<td>Sleeve</td>
<td>1.4 ± 0.36</td>
<td>4.5 ± 0.72</td>
<td>5.4 ± 0.25</td>
</tr>
<tr>
<td>Wet swallows both catheters</td>
<td>HREPT</td>
<td>1.2 ± 0.27</td>
<td>4.5 ± 0.79</td>
</tr>
<tr>
<td>Sleeve</td>
<td>2.0 ± 0.39</td>
<td>3.9 ± 0.32</td>
<td>5.8 ± 0.33</td>
</tr>
<tr>
<td>TLESRs</td>
<td>HREPT</td>
<td>0.8 ± 0.12</td>
<td>3.8 ± 0.14</td>
</tr>
<tr>
<td>Sleeve</td>
<td>0.1 ± 0.08</td>
<td>4.2 ± 0.19</td>
<td>17.3 ± 0.51</td>
</tr>
</tbody>
</table>

TABLE 1 | Wet swallow and TLESR characteristics. LES characteristics during wet swallows do not differ with one or with two catheters.
TLESRs associated with Reflux

A total of 143 reflux episodes were detected by MII-pH, of which 138 occurred during a TLESR (97%). Of all TLESRs recorded by both methods (177), 78% was accompanied by a reflux event. TLESRs accompanied by reflux were significantly more detected by HREPT (132) compared to sleeve manometry (119) (P=0.015). The sensitivity for the detection of TLESRs associated with reflux increases from 86% for sleeve manometry to 96% for HREPT, in comparison to all reflux episodes during TLESRs detected. The refluxate acidity and content characteristics are shown in Figure 1. Of all reflux episodes 16% was acid, 76% was weakly acid and 8% was non acid. There was no difference in the number of TLESRs with an acid reflux episode detected (21 for HRM vs 18 for sleeve manometry (P=NS)). TLESRs that were detected by both techniques but not accompanied by reflux (N=14) were not different from TLESRs accompanied by reflux regarding nadir pressure or TLESR duration.

Analysis of ‘missed’ TLESRs

Nineteen TLESRs accompanied by reflux were missed by sleeve manometry. Analysis of these episodes in sleeve manometry showed that 1. the sleeve sensor did not reach a nadir pressure of 2 mmHg (n=10) (Figure 2), 2. TLESRs occurred during periods of low basal LES pressure and were missed (n=5) (Figure 3) 3. unstable pharyngeal signal or multiple swallows influenced the tracing (n=4). Six TLESRs accompanied by reflux were missed by HREPT due to 1. an unclear start of the TLESR relative to the onset of a swallow (n=2) 2. a nadir pressure above 2 (n=2) 3. a relaxation rate of < 1 mmHg(n=1) 4. erroneously missed by two of three authors (n=1). Nadir pressure of more than 2 mmHg during a TLESR with reflux was more seen using sleeve manometry than using HREPT (10 vs 2, P<0.05). During low LES pressure, TLESRs with reflux were more often missed by sleeve manometry than HREPT (5 vs 0, P<0.05).
FIGURE 2 | A TLESR with reflux, that was missed by sleeve manometry, due to high residual pressure in the sleeve (nadir is 5 mmHg measured by sleeve). The "vSleeve", a functional tool of HREPT software, shows a similar tracing to the water perfused sleeve. The positioning of the vSleeve is important for the nadir, which can be appreciated in tracing A and B: A.) When a vSleeve of 6 cm, similar to the original sleeve, is used the nadir pressure is 4 mmHg. B.) With a more precise identification of the LES the vSleeve tracing has a nadir pressure of 1 mmHg, and a TLESR can be scored.

FIGURE 3 | Esophageal shortening, as seen by HREPT. The cranial movement of the LES can be followed by the closely spaced pressure sensors. In this TLESR, the upper border of the LES moves 6.6 cm cranially, while the upper esophageal sphincter remains in the same position and contracts, with a subsequent esophageal shortening of 6.6 cm.
Esophageal shortening
Mean shortening during TLESRs detected with HREPT was 3.0 ± 0.11 cm compared to 1.2 ± 0.10 cm during wet swallows (P<0.001). (Figures 3 and 4) The maximum esophageal shortening during peristalsis after wet swallows was 3 cm, versus 7 cm for TLESRs. Esophageal shortening was greater during TLESRs with reflux than during those without (3.1 ± 0.11 cm vs 2.5 ± 0.26 cm P<0.05). TLESRs with reflux missed by sleeve manometry had a mean shortening of 3.1 ± 0.30 cm, and a shortening of more than 2 cm was seen in 13 out of 19 of these TLESRs.

FIGURE 4 | Esophageal Shortening.

DISCUSSION
This study compared HREPT and sleeve manometry for the detection of TLESRs. The detection rate of all TLESRs was comparable for HREPT and sleeve manometry. However, TLESRs accompanied by a reflux event were significantly more detected using HREPT. Based on these findings, we suggest that HREPT is the method of choice to detect TLESRs.

Reflux events are best detected by impedance, and their acidity characterised by pH-metry.\textsuperscript{12} MII-pH monitoring detects acidic, weakly acidic reflux, and gas reflux, and is therefore currently considered the gold standard for the detection of reflux events.\textsuperscript{21,23} In this study, MII-pH was used to compare HREPT to sleeve manometry. We showed that the sensitivity to detect TLESRs with reflux increased from 86% for sleeve manometry to 96% for HREPT. Our results are comparable to the study of Bredenoord et al. that compared closely spaced water perfused sideholes to a sleeve sensor for the detection of TLESRs.\textsuperscript{19} In that study, criteria were slightly modified and were applied
to the two tracings with the highest pressure values at the level of the LES. In recent studies performed with HREPT, the original criteria as defined by Holloway et al. for sleeve manometry were used for detection of TLESRs. The comparison in our study shows that the use of these criteria leads to a comparable detection rate, and thus can indeed be used for HREPT.

The four main conditions in which HREPT is superior to sleeve manometry to detect TLESRs are:
1. an increased resolution at the level of the LES that reveals LES opening in detail
2. an increased detection during periods of low basal LES pressure,
3. the detection of esophageal shortening, and
4. the improved detection of reflux during a TLESRs (increased esophageal pressure resulting from reflux). In the first condition, a high residual LES pressure is seen in TLESRs with reflux detected by HREPT but missed by sleeve manometry. Detailed analysis of the HREPT tracings revealed that the EGJ relaxation during a TLESR is not homogeneous with some parts maintaining some residual pressure above 2 mmHg. Indeed, the gastric sling or the crural diaphragm do not always open instantaneously, and completely relax only during a short period of time. Furthermore, contraction of the lowest part of the esophagus while the LES is relaxed can be picked up by the sleeve sensor. As the sleeve detects the highest pressure along its length, this small segment of persistent pressure will result in a residual pressure at sleeve manometry above the cut off value of 2 mmHg and thus will not be scored as a TLESR. To confirm this hypothesis, we used the virtual sleeve function (vSleeve). This part of the software integrates all pressure values at the level of the LES to one tracing, mimicking the function of the sleeve. As shown in figure 2 a similar tracing to the original sleeve sensor tracing is seen, with a similar residual LES pressure above 2 mmHg, when a vSleeve of 6 cm is used. The second condition in which HREPT is superior to the sleeve is during periods of low LES pressure. (figure 3) Detection of TLESRs is indeed more difficult during episodes of low LES pressure, and moreover, the criterion that pressure has to drop faster than 1 mmHg per second is more difficult to fulfill. The advantages of HREPT may therefore be even more pronounced in GERD patients, who more often have a low basal LES pressure. The third condition leading to improved detection of TLESRs by HREPT is the detection of esophageal shortening. Shortening can be clearly appreciated during TLESRs and wet swallows. In contrast to swallowing, esophageal shortening during a TLESR is much more pronounced, even up to 7 cm (Figures 3 and 4). Comparable findings have been described previously by Pandolfino et al. Esophageal shortening facilitated recognition of TLESRs in 13 out of 19 events with reflux missed by sleeve manometry.

The last condition which leads to an improved detection rate is the pressure increase in the esophageal body during a reflux event. Although there is some debate whether this pressure increase is a consequence of esophageal shortening or the occurrence of reflux, in healthy volunteers both are only seen during TLESRs. In 13 out of 19 TLESRs with reflux missed by
conventional manometry there was a pressure increase in the esophageal body, whereas this pressure increase (common cavity) was only seen in 4 of these TLESRs in conventional manometry. TLESRs are therefore more easily picked up, and this explains why especially TLESRs with reflux are better detected by HREPT. Both esophageal shortening and esophageal pressurisation are however no criteria for detection of TLESRs. Therefore, specific criteria for HREPT are still awaited. It needs to be emphasized that there is no gold standard for the detection of TLESRs, which complicates the validation of a new technique. In this study we have assumed that events only detected by HREPT that met Holloway criteria and have a reflux episode were TLESRs. Supportive to our assumption is the clear esophageal shortening during these events, which is only seen during TLESRs as was shown in multiple studies. 20, 27

In conclusion, detection rate for TLESRs is equal for HREPT and sleeve manometry, and this study thereby shows that HREPT is suitable for detection. The increase in detection rate for TLESRs with reflux is mainly explained by the higher spatial resolution at the level of the LES and the precise positioning of the vSleeve, the increased detection rate during low basal LES pressure and the visualisation of esophageal shortening and gastroesophageal reflux. The additional value of HREPT for the detection of TLESRs in patients was not investigated in this article. Patients with GERD and healthy volunteers are regarded to have comparable numbers of TLESRs, but one can hypothesize that the beneficial effect of HREPT is even larger in GERD patients, due to a lower basal LES pressure. Further studies on this topic are awaited to confirm this assumption.
REFERENCE LIST


