Towards better understanding of symptoms associated with disordered esophageal function
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Citation for published version (APA):
Herregods, T. V. K. (2017). Towards better understanding of symptoms associated with disordered esophageal function

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SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES
SUMMARY

Gastroesophageal reflux disease (GERD) is one of the most common disorders of the gastrointestinal tract. GERD is associated with a large range of symptoms, which can be split into the typical and atypical reflux symptoms. Heartburn and regurgitation are considered to be typical reflux symptoms while atypical symptoms comprise non-cardiac chest pain, chronic cough, dysphagia, hoarseness, globus and throat irritation. This thesis aimed to address some of the unanswered questions in the pathophysiology and diagnosis of gastroesophageal reflux disease, also including reflux-associated chronic cough, non-cardiac chest pain and dysphagia.

In chapter 2 we describe a study in which we investigated the underlying cause of reflux symptoms not or insufficiently responding to proton pump inhibitor (PPI) therapy in tertiary referral patients. In this retrospective study we evaluated 106 patients with PPI-refractory reflux symptoms using 24-hour pH-impedance monitoring after cessation of acid suppressive therapy. In all patients esophagitis and Barrett’s esophagus were ruled out with gastroscopy, and esophageal manometry was carried out prior to the 24-hour ambulatory pH-impedance measurement. Interestingly, we found that approximately a third of the patients with a negative gastroscopy do not have GERD but instead suffer from other disorders, predominantly functional heartburn. Therefore, the presence of refractory reflux symptoms does not equate to refractory GERD. It is important to make the distinction as treatment options differ. Furthermore we confirmed the importance of esophageal manometry in patients with refractory reflux symptoms as two patients ended up with a diagnosis of achalasia and one patient had rumination syndrome.

In chapter 3 we investigated the effect of running on reflux severity and examined the underlying reflux mechanisms. This prospective study was carried out in 10 healthy sporty volunteers who were studied using both high-resolution manometry (HRM) and pH-impedance monitoring while they ran on a treadmill. The exercise protocol included a medium- and a high-speed running period, separated by a short resting period. Exercise resulted in a significantly higher acid exposure (percentage of time with pH<4). We demonstrated that this increase is caused by both an increase in the frequency of reflux episodes as well as an increase in the duration of individual reflux episodes. Interestingly, reflux episodes occurred almost exclusively during transient lower esophageal sphincter relaxations (TLESRs). Akin to the situation in GERD patients, we found that TLESRs were not more frequent but were more often associated with a reflux episode. Furthermore, 60% of the subjects developed a hiatus hernia during exercise which was not seen during the resting state. It is therefore likely that exercise results in a change of esophagogastric junction (EGJ) morphology resulting in an increase in reflux during TLESRs. It seems therefore that exercise induces changes in healthy subjects that resemble abnormalities encountered in patients with GERD. We also found that the contractility of the esophageal body was
decreased during the heavy exercise period which resulted in a higher proportion of the standardized wet swallows to be failed. As a result, one of the protective mechanisms against reflux, the clearance of acid from the esophagus by esophageal peristalsis, could be limited during exercise and thus result in an increased reflux time.

In chapter 4, 5 and 6 we investigated the reflux-cough interrelationship in patients with chronic unexplained cough. Two main pathophysiological mechanisms have been suggested for reflux-induced cough. The first is that the refluxate triggers a cough reflex through stimulation of a vagally mediated esophagobronchial reflex. The second theory suggests that (micro)aspiration of gastric content stimulates the afferent limb of a cough reflex initiated by irritating the respiratory tract. To evaluate patients suspected of having reflux-induced cough, 24-hour pH-impedance-pressure monitoring can be used. A two-minute time window is generally used when evaluating patients with chest pain and typical reflux symptoms. This two-minute time window was originally established to assess the temporal association between reflux and chest pain, and therefore it was unclear whether this time window is also optimal when evaluating patients with chronic cough. In chapter 4 we investigated 137 patients with chronic cough using 24-hour pH-impedance-pressure monitoring. We employed repetitive symptom association analysis with an array of time windows of various duration. For each of the time windows the symptom association probability (SAP) and the symptom index (SI) were calculated. We found that a two-minute time window seems appropriate for the evaluation of the relationship between reflux and chronic cough. Furthermore, we found that a time window duration of 30 seconds or 1 minute would be too short to diagnose reflux-induced cough accurately. This suggests that the theory that (micro)aspiration is the primary pathophysiological mechanism is less likely as one would expect a short duration between (micro)aspiration and cough onset.

In chapter 5 we assessed the importance of 24-hour ambulatory pH-impedance-pressure monitoring in finding a causal relationship between chronic cough and reflux. In this multicenter retrospective study we evaluated 192 patients with chronic cough using 24-hour pH-impedance-pressure monitoring off PPIs. The manometry catheter was used to detect all the cough bursts while the pH-impedance allowed for the evaluation of all reflux episodes. The SAP was used to determine a temporal relationship between reflux and cough. We found that only approximately one quarter of the patients with chronic unexplained cough has reflux-induced cough, which helps to explain the observation that the vast majority of patients with chronic cough does not benefit from anti-reflux therapy. Furthermore we demonstrated that it is important to use 24-hour pH-impedance monitoring combined with objective detection of cough episodes to identify patients who are likely to have reflux as a cause of their chronic cough. Impedance measurement has the additional benefit of detecting weakly acidic reflux episodes which are shown to be important in this
patient population, and the objective detection of cough bursts is important because patients only register approximately 59% of all the cough bursts.

In chapter 6 we aimed to understand why some reflux episodes in the same patient cause cough while others do not. In this multicenter study, 49 patients with reflux-associated chronic cough were analyzed using 24-hour pH-impedance-pressure monitoring. We compared the characteristics of reflux episodes which were followed by cough with those which were not. We found that reflux episodes which were followed by a cough burst were associated with a higher proximal extent, a higher volume clearance time, and a higher acid burden in the preceding 15-minute window and higher reflux burden in the preceding 30-minute window. Furthermore we found that acidity plays a less crucial role in reflux-induced chronic cough than in the genesis of typical reflux symptoms. Instead, a larger volume of refluxate and prolonged esophageal exposure to reflux seemed to play a major role in inducing a cough burst. Moreover, we demonstrated that the reflux burden is an important determinant in cough induction which suggests that reflux may sensitize the esophagus for subsequent reflux episodes. Furthermore, this suggests that central sensitization or an esophagobronchial reflex is a more likely pathophysiological mechanism than microaspiration of refluxate.

In chapter 7 and 8 we evaluated patients with non-cardiac chest pain (NCCP). In chapter 7 we aimed to evaluate the importance of 24-hour pH-impedance monitoring in NCCP patients and to understand why some reflux episodes in the same patient cause chest pain while others do not. In this multicenter study, 120 patients were included who underwent 24-hour pH-impedance monitoring. In the 15 patients with a positive association between reflux and chest pain, we compared the characteristics of the reflux episodes which were followed by chest pain with those which were not. The importance of 24-hour pH-impedance monitoring in NCCP patients is underlined by the finding that in 40% of the NCCP patients gastroesophageal reflux was a possible cause of their chest pain. Furthermore, we found that, compared with reflux episodes which were not followed by chest pain, reflux episodes which were associated with chest pain had a higher proximal extent, a higher volume clearance time, were more often acidic, had a lower nadir pH and had a longer acid duration time. Therefore, similar to the perception of typical reflux symptoms, the acidity of the refluxate appears to be important in perceiving a reflux episode as chest pain. Furthermore, the data indicate that the presence of a larger volume of refluxate for a longer period of time plays an important role in perceiving a reflux episode as chest pain. Finally, we demonstrated that the presence of typical reflux symptoms increases the likelihood that GERD is the cause of the chest pain.

In chapter 8 we assessed the additional yield of ambulatory manometry to stationary high-resolution manometry (HRM) and ambulatory pH-impedance monitoring in patients with NCCP. In this retrospective study, we analyzed 59
NCCP patients who had undergone both HRM and 24-hour ambulatory pressure-pH-impedance monitoring. The isolated diagnostic yield of ambulatory 24-hour manometry for esophageal spasm was only 6.8%. Using the Chicago classification v3.0 criteria alone, HRM did not identify any of the 4 patients with esophageal spasm on ambulatory manometry. However, when 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. We concluded that in the work-up of NCCP, ambulatory 24-hour manometry has a low additional diagnostic yield, yet it remains the best technique to identify esophageal spasm as the cause of symptoms. Furthermore, it allows 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.

In chapter 9 we described a large cohort of patients with jackhammer esophagus and investigated whether manometric findings were associated with the presence of symptoms. In this multicenter retrospective study, we identified 34 patients with jackhammer esophagus of whom approximately two-thirds suffered from dysphagia and almost half from chest pain. We found no association between the symptom chest pain and any of the manometric findings, while dysphagia was associated with the distal contractile integral (DCI) of the hypercontractile swallows and with the intrabolus pressure. Moreover, all patients with an isolated DCI of the lower esophageal sphincter zone > 2000 mmHg·s·cm had dysphagia, and EGJ outflow obstruction was present in 20.6% of the patients. Furthermore we found only limited differences in clinical or HRM characteristics between subgroups based on the contraction type (single- or multi-peaked) or based on meeting criteria of the Chicago classification v3.0 and v2.0. We concluded that the symptom dysphagia is accompanied with strong contractions of the lower esophageal sphincter, signs of a possible outflow obstruction, and a very high DCI. In addition, the presence of a multipeaked contraction seems to be of limited relevance, and caution is warranted in labeling patients with one hypercontractile swallow as normal.

In chapter 10 we evaluated whether subtle motor abnormalities, visualized with HRM, could explain the dysphagia in a subset of patients with non-obstructive esophageal dysphagia and normal esophageal motility according to the Chicago classification v3.0. In this study we compared HRM parameters of LES relaxation in healthy volunteers to those of patients with unexplained non-obstructive esophageal dysphagia. We found a significantly longer interval between swallow and LES relaxation in the patients compared to the healthy controls. We calculated normative values based on the healthy volunteers and found that approximately one quarter of the patients with dysphagia had a delayed and/or incomplete LES relaxation.
Furthermore, patients with delayed and/or incomplete LES relaxation had a significantly higher intrabolus pressure compared to patients with normal relaxation, suggesting that during these suboptimal LES relaxations, the flow across the esophagogastric junction is hindered. We concluded that subtle LES relaxation abnormalities, such as delayed and/or incomplete LES relaxation, is a potential cause of dysphagia in approximately one quarter of patients with non-obstructive esophageal dysphagia in whom conventional analysis of HRM does not yield any abnormalities.

**DISCUSSION AND FUTURE PERSPECTIVES**

We believe that the studies described in this thesis have provided relevant new information on some aspects of the pathophysiology and diagnosis of patients with gastroesophageal reflux disease (GERD), chronic cough, non-cardiac chest pain and dysphagia. However, there are still many remaining questions which need to be addressed.

**Pathophysiology**

In patients with GERD some factors promote the occurrence of reflux by weakening the physiological defense mechanisms, while other factors increase the perception of the refluxed gastric content. Both hiatal hernia1-3 and transient lower esophageal sphincter relaxations (TLESRs)4,5 have been shown to be of great importance in the pathophysiology of GERD.

In chapter 3 we demonstrate that running leads to a statistically significant increase in esophageal acid exposure in healthy volunteers. Previously6, it was assumed that the increase in total reflux time during exercise could be the result of more frequent episodes in which the abdominal pressure exceeds the esophagogastric junction (EGJ) pressure. Our analysis does show a decrease in the minimum EGJ pressure and an increase in the abdominal pressure during exercise, which would support this notion. Nevertheless, we found that all but one reflux episode occurred during TLESRs, and that, like in patients with GERD7,8, the frequency of TLESRs did not increase but instead the proportion of TLESRs associated with reflux was elevated. Moreover, we found that heavy exercise resulted in a decrease in wet swallow-induced esophageal contractility and delayed acid clearance. This supports previous studies which found an altered esophageal motility during exercise9,10. Interestingly, we also found that in 60% of the subjects a hiatus hernia was present during exercise which was not seen during the resting state. Therefore we concluded that exercise induces changes in healthy subjects which resemble abnormalities encountered in patients with GERD. Our results suggest that future therapy in patients with reflux complaints during exercise who do not benefit from proton pump inhibitor (PPI) therapy could consist of drugs that inhibit TLESRs. In addition, in the light of the increased duration
of reflux episodes found during exercise, future therapy which enhances esophageal motility could have a beneficial effect. Unfortunately, the development of TLESR inhibitors and esophagus-specific prokinetic drugs has not been very successful thus far. It is hoped that pharmaceutical industries will renew their efforts to develop these drugs, not only to combat exercise-induced reflux, but also to treat patients with PPI-refractory symptoms.

In patients with chronic unexplained cough, GERD is considered to be one of the most important contributing factors\textsuperscript{11}. Two pathophysiological mechanisms have been suggested for reflux-induced cough. The first is that refluxate triggers a cough reflex through stimulation of a vagal esophagobronchial reflex. The second theory suggests that (micro)aspiration of gastric content can stimulate the afferent limb of the cough reflex by irritating the respiratory tract, initiating a sequence leading to cough\textsuperscript{11}. If the latter is correct, it seems logical to assume that the duration between the aspiration of the refluxed content and the cough is shorter than 2 minutes. This is supported by the European Respiratory Society guideline on the assessment of cough which suggests that when the single-breath method of capsaicin and citric acid is used as a cough challenge, only coughs that occur within 15 seconds after delivery should be counted\textsuperscript{12}. In chapter 4 we found that a time window duration of 30 seconds or 1 minute would be too short to reliably diagnose patients with reflux-induced chronic cough. Even though this does not totally exclude the possibility that (micro)aspiration is a pathophysiological mechanism, as many patients still had a positive association when short time windows were used, it does suggest that stimulation of an esophagobronchial reflex is more important. In chapter 6 we aimed to understand more about the mechanism by which reflux induces cough. We demonstrate that reflux episodes which were followed by cough were not more frequently acidic, did not have a lower nadir pH, a larger pH drop, or a longer acid clearance time compared to reflux episodes which were unrelated to cough. This suggests that acidity of the refluxate is not a key factor in inducing cough bursts. Moreover, we found a trend towards a higher 15-minute “reflux burden” and a significantly higher 30-minute reflux burden. This suggests that the time that the refluxate is present in the esophagus is more important than the time that acid is present and therefore the quantity of the refluxate, or a non-acidic component of the refluxate, could be an important factor. These observations may help to explain the limited efficacy of acid-inhibitory medication in placebo-controlled trials\textsuperscript{13,14}, and support the notion that refluxate sensitizes the esophagus to subsequent reflux episodes. As in chapter 4, we conclude that (micro)aspiration of gastric content is less likely to be the primary pathophysiological mechanism of reflux-induced cough. This is further supported by the finding that reflux episodes only reaching the distal esophagus were still able to trigger cough. It could be argued that miniscule traces of reflux could still reach the respiratory tract leading to micro-aspiration, yet this would not explain why most
reflux episodes reaching the proximal esophagus did not result in cough. In addition, we showed that most coughs were not temporally associated with reflux. This supports the notion that cough could be self-perpetuating due to central processes, or that multiple mechanisms may operate in an individual patient. The importance of central mechanisms is supported by studies which have shown an improvement in cough frequency and severity upon treatment with gabapentin, a centrally active drug. Another possibility, suggested in an article by Kahrilas et al., is that reflux is just another one of the aforementioned stimuli and that the sensitization is the result of another mechanism. Our study shows that volume rather than acidity seems to be important in patients with reflux-induced cough, which could explain why anti-reflux surgery seems to be more effective than medical treatment. Since sensitization appears to be an important factor, future studies should evaluate whether medication targeting this sensitisation, such as amitriptyline or citalopram, has a beneficial effect in patients with reflux-induced cough. Furthermore, interventions which decrease the quantity of the refluxate rather than reducing its acidity deserve exploration as they might aid in treating these patients in the future.

GERD is the most common gastrointestinal cause of NCCP, with many studies showing an association between NCCP and GERD. It is important to note that the relationship between gastroesophageal reflux and NCCP is complex. It remains unclear why some reflux episodes in the same patient cause chest pain while others do not. In chapter 7 we compared reflux episodes which were associated with chest pain with reflux episodes which were not in patients with a positive association for reflux-associated chest pain. Similar to the 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 acidity is important in perceiving a reflux episode as chest pain, but also the duration of time that the acid is present in the esophagus. This is in contrast to the findings in chapter 6, and suggests that unlike in chronic cough, the reflux characteristics of reflux episodes causing typical reflux symptoms and chest pain are similar. We also 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. This could be due to some patients having a more reflux-sensitive proximal esophagus. Previously it has been shown that infusion of hydrochloric acid into the distal esophagus over 30 minutes lowered the pain threshold to electrical stimulation in the upper esophagus. 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 could be 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{26-29}.

With the advent of high-resolution manometry (HRM), a new diagnosis, jackhammer esophagus, was introduced. Little is known about this rare condition, and the relationship between symptoms and hypercontractility is not always straightforward. In chapter 9 we evaluated patients with jackhammer esophagus and found no association between any of the manometric findings and the symptom chest pain. This suggests that chest pain is not clearly linked to the finding of jackhammer esophagus, which in turn could explain why some patients do not respond to treatment such as nitrates and calcium channel blockers. Another potential explanation is that chest pain could be the result of other factors such as ischemia\textsuperscript{30} or an increased muscle thickness which is not visualized using HRM. Future research could focus on the link between chest pain and jackhammer esophagus. In our study we did find an association between dysphagia and the DCI of the hypercontractile swallows. This suggests that despite the normal distal latency seen in these patients, the very high-DCI swallows might not result in the proper clearance of the esophagus or that the high-amplitude contraction itself results in a sensation of incomplete passage. Indeed, the relationship between bolus passage and contractility is poor\textsuperscript{31}. Another possibility is that the high contractility is secondary and necessary to overcome an outflow obstruction. Previously it has already been suggested that hypercontractility could be caused by EGJ obstruction\textsuperscript{32}. In the opossum, experimental EGJ obstruction resulted in smooth muscle hypertrophy and excitability\textsuperscript{33}. In humans, inflation of an implanted band at the EGJ was found to produce an acute increase in esophageal contractility\textsuperscript{34}. The hypothesis is that the lack of LES relaxation causes an obstruction to the flow through the EGJ, increasing the intrabolus pressure and resulting in hypercontractility. In our study we found that the DCI correlated with the integrated relaxation pressure (IRP) of the hypercontractile swallows and with the IBP, supporting the idea that an outflow obstruction or a lack of LES relaxation results in hypercontractility. Therefore, in this subset of patients it could be beneficial to start with the treatment of the underlying EGJ outflow obstruction rather than attempting to treat the hypercontractility with e.g. calcium channel antagonists or nitrates.

**Diagnosis**

Several diagnostic tests can be used to diagnose a patient with GERD, including a PPI test, esophagogastroduodenoscopy and 24-hour pH-impedance monitoring.
In tertiary referral gastrointestinal practices reflux symptoms refractory to PPIs has become one of the major predicaments. Using combined esophageal pH-impedance monitoring it has been shown that refractory symptoms are often associated with weakly acidic reflux events\textsuperscript{35,36}. Moreover, visceral hypersensitivity has been suggested to contribute to symptom perception\textsuperscript{37} and thus to PPI-resistant symptoms in these patients. In chapter 2 we demonstrate the importance of distinguishing the NERD patients from the patients with functional heartburn. Using pH-impedance monitoring, approximately a third of the patients with a negative gastroscopy was found to have a diagnosis of functional heartburn (30.2%) or functional chest pain (1.9%). Moreover, we demonstrate the importance of esophageal manometry in patients with refractory symptoms as 2 of the 106 patients had a primary diagnosis of achalasia and one patient had rumination syndrome. These patients do not have GERD and would certainly not benefit from the typical approach of dose escalation or surgery. They require a different treatment. Our study thus provides evidence that function testing consisting of pH-impedance monitoring and esophageal manometry, is beneficial in patients with refractory GERD symptoms as results could alter the therapeutic approach significantly. The use of visceral pain modulators, such as tricyclic antidepressants, is generally accepted as treatment for patients with functional heartburn, even though the clinical trials to support this are currently lacking. The pathophysiology of functional heartburn and functional chest pain is still very obscure. It is to be expected that, once future studies have yielded more insight into the pathophysiology of these conditions, new therapeutic options can be explored.

Although there is consensus about the existence of a reflux-cough syndrome\textsuperscript{38}, it is difficult to establish the diagnosis in individual patients. In previous studies\textsuperscript{15,39-41} reflux episodes were considered to be associated with cough bursts if they occurred within a two-minute time window before the onset of the cough burst. However, it remains unclear whether this two-minute time window, which was originally established to assess the association between reflux and chest pain, and which was never tested for reflux-induced cough, can be carried over to this indication. In chapter 4 we demonstrate that a window of approximately two minutes seems appropriate for the assessment of the reflux-cough association in patients with the reflux-cough syndrome. Moreover, as can be expected, a diagnosis of reflux-induced cough based on a symptom association probability (SAP) > 99% is more robust. Furthermore, we show that many patients clearly lack an association between reflux and cough and, in these, the possibility of reflux-induced cough can be confidently dismissed. In chapter 5 we demonstrate the importance of rigorous patient selection through the use of 24-hour ambulatory pressure-pH-impedance monitoring in patients with chronic unexplained cough as in only approximately a quarter of the patients a diagnosis was made of reflux-induced chronic cough. This could explain the low treatment efficacy\textsuperscript{13,14} and helps to show the value of 24-hour ambulatory
pH-impedance-pressure monitoring in determining which patients could benefit from acid suppressive treatment. Moreover, the usefulness of adding impedance to the pH-monitoring is emphasized by the importance of detecting weakly acidic reflux episodes in these patients, supporting the results of a previous study41. Furthermore, we demonstrate that objectively detecting the cough bursts is important and that even though the presence of typical GERD symptoms and pathological distal acid exposure time are associated with an increased chance of having reflux-induced cough, many patients will be missed if these criteria alone are used to identify patients who are likely to respond to treatment. Future placebo-controlled studies should evaluate the effect of acid inhibitory treatment in patients who showed a positive association for reflux-induced cough on 24-hour pH-impedance-pressure monitoring rather than including all patients in whom reflux is thought to be the cause of the chronic cough. Likewise, future studies should explore the predictive value of a positive reflux-cough association for a beneficial effect of interventions that diminish all types of reflux, for instance laparoscopic fundoplication.

Non-cardiac chest pain can be the result of GERD, esophageal dysmotility, psychiatric disease such as panic attacks, and musculoskeletal pain42. GERD is the most common gastrointestinal cause of NCCP20. In chapter 7 and 8 we demonstrate the importance of evaluating NCCP patients with 24-hour pH-impedance monitoring as a reflux-related origin of the symptoms was found in more than a third of the patients. Moreover, in chapter 8, we show that 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. 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 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 latency43. Moreover, our study suggests that 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.

With the advent of HRM, a new diagnosis, jackhammer esophagus, was introduced. Most patients with jackhammer esophagus suffer from dysphagia and/or chest pain. In chapter 9 we evaluate a large cohort of patients with jackhammer esophagus. In our study we found that the patients who met the Chicago classification v2.0 criteria
but not the Chicago classification v3.0 criteria did not differ in clinical characteristics to those who did meet the Chicago classification v3.0 criteria. Moreover, besides the distal contractile integral (DCI), the HRM parameters did not differ significantly. We argue that the finding of one swallow with a DCI > 8000 mmHg·s·cm remains rare in healthy controls, and that since these groups are very similar in both clinical characteristics and in HRM metrics, caution is warranted in labeling patients with one swallow with a DCI > 8000 mmHg·s·cm as normal. The relevance of multi-peaked contractions has previously been studied in jackhammer patients\textsuperscript{32}. As in the study by Roman et al.\textsuperscript{32}, 88.2% of our patients with jackhammer esophagus had multi-peaked contractions, of which half were synchronized with respiration. We also found that most of the HRM characteristics were not dependent on the presence of respiratory synchronization or multi-peak contractility. Due to the lack of substantial differences between the subgroups, this distinction seems to be of limited relevance. Future studies should investigate whether hypervigorous contractions persist despite the alleviation of symptoms, and what the best treatment options are.

The advent of HRM also resulted in a new objective measurement of the EGJ relaxation, namely the IRP\textsuperscript{44,45}. This is of importance in patients with dysphagia who are suspected of having a functional obstruction or another esophageal motility problem which could explain the symptom. In the absence of structural, mucosal, or motor abnormalities to explain the symptom, a diagnosis of functional dysphagia is made\textsuperscript{46}. In chapter 10 we evaluate whether subtler forms of dysfunction of the LES can be visualized on HRM, as many patients with dysphagia do not meet the Chicago criteria for a motility disorder. We found that 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 potential 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). It is conceivable that a delay in the opening of the LES could result in the symptom dysphagia as in the upright position, the leading edge of a liquid bolus can reach the LES soon after swallowing\textsuperscript{47}. Future studies can evaluate whether these findings are of clinical importance as these patients could benefit from different treatment options.
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