Diagnostic yield of high-resolution manometry with a solid test meal for clinically relevant, symptomatic oesophageal motility disorders: serial diagnostic study

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Summary

Background The use of high-resolution manometry (HRM) to diagnose oesophageal motility disorders is based on ten single water swallows (SWS); however, this approach might not be representative of oesophageal function during the ingestion of normal food. We tested whether inclusion of a standardised solid test meal (STM) to HRM studies increases test sensitivity for major motility disorders. Additionally, we assessed the frequency and cause of patient symptoms during STM.

Methods Consecutive patients who were referred for investigation of oesophageal symptoms were recruited at Nottingham University Hospitals (Nottingham, UK) in the development study and at University Hospital Zürich (Zürich, Switzerland) in the validation study. HRM was done in the upright, seated position with a solid-state assembly. During HRM, patients ingested ten SWS, followed by a standardised 200 g STM. Diagnosis of oesophageal motility disorders was based on the Chicago Classification validated for SWS (CCv3) and with STM (CC-S), respectively. These studies are registered with ClinicalTrials.gov, numbers NCT02407938 and NCT02397616.

Findings The development cohort included 750 patients of whom 360 (48%) had dysphagia and 390 (52%) had reflux or other symptoms. The validation cohort consisted of 221 patients, including 98 (44%) with dysphagia and 123 (56%) with reflux symptoms. More patients were diagnosed with a major motility disorder by use of an STM than with SWS in the development set (321 [43%] patients diagnosed via STM *vs* 163 [22%] via SWS; p<0·0001) and validation set (73 [33%] *vs* 49 [22%]; p=0·014). The increase was most evident in patients with dysphagia (241 [67%] of 360 patients on STM *vs* 125 [35%] patients on SWS in the development set, p<0·0001), but was also present in those referred with reflux symptoms (64 [19%] of 329 patients *vs* 32 [10%] patients in the development set, p=0·00060). Reproduction of symptoms was reported by nine (1%) of 750 patients during SWS and 461 (61%) during STM (p<0·0001). 265 (83%) of 321 patients with major motility disorders and 107 (70%) of 152 patients with minor motility disorders reported symptoms during the STM (p=0·0038), compared with 89 (32%) of 277 patients with normal motility as defined with CC-S (p<0·0001).

Interpretation The diagnostic sensitivity of HRM for major motility disorders is increased with use of the STM compared with SWS, especially in patients with dysphagia. Observations made during STM can establish motility disorders as the cause of oesophageal symptoms.

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Introduction

Swallowing difficulties and symptoms related to gastro-oesophageal reflux disease are common in the community,[1,2] and are a common reason for specialist referral. The aim of oesophageal investigation is to identify the causes of symptoms, establish a diagnosis, and guide treatment. Upper gastrointestinal endoscopy and radiology are unable to identify pathology in at least half of patients with dysphagia and treatment-resistant reflux symptoms, requiring further investigation to assess oesophageal motility and function.[3,4] High-resolution manometry (HRM) data collected during ten single water swallows (SWS) are used in accordance with the Chicago Classification (CC) to diagnose oesophageal motility disorders.[5,6] However, in many patients, even this advanced technology cannot identify the cause of symptoms or provide a definitive diagnosis.[7–9] One plausible explanation is that HRM studies based on SWS might not be representative of swallowing function during a normal meal.

Manometry studies have shown differences between water, viscous, and solid swallows in healthy volunteers[10] and in patients.[11] Case series data suggest that ingestion of solids increases the sensitivity of manometry for motility disorders;[8,10–20] however, in a prospective study, the addition of viscous and a small number of solid swallows to the protocol was found not to have a significant effect on diagnosis.[21] In an accompanying Article,[22] we present a method to analyse oesophageal motility during a solid test meal (STM). Reference ranges are provided for healthy controls and compared with pathological findings in well characterised patients with motility disorders. The primary aim of this study was to test the hypothesis that the addition of STMs to clinical HRM studies increases

Research in context

Evidence before this study

The Chicago Classification version 3 (CCv3) of oesophageal motility disorders for high-resolution manometry (HRM) is based on objective metrics from ten single water swallows (SWS). CCv3 is a consensus document based on the totality of evidence available at the time it was written. Results from pilot studies suggest that inclusion of solid swallows improves diagnostic yield of HRM for motility disorders; however, clinical evidence from large patient series is not available. In an accompanying Article, we present methods for the assessment of oesophageal motility during a solid test meal (STM) and reference values for normal controls with the Chicago Classification adapted for use with solid swallows (CC-S).

Added value of this study

This is the first, large, clinical study to assess the impact of including an STM on the diagnostic yield of routine HRM studies in patients referred for investigation of oesophageal symptoms. Compared with standard measurements based on SWS only, inclusion of the STM increases diagnostic yield for major motility disorders, especially for oesophagogastric junction outlet obstruction. Additionally, this method identifies patients with symptomatic minor motility disorders. The clinical relevance of findings during the STM is supported by the close temporal association of abnormal motility with patient symptoms in more than three-quarters of patients with motility disorders.

Implications of all the available evidence

This paper shows the clinical utility of the addition of an STM in routine HRM studies. This method combines ease of use, minimal expense, and high patient acceptance, leaving few barriers to its implementation in clinical practice.

test sensitivity for major motility disorders. The secondary aim was to assess whether observations during the STM could establish the cause of symptoms.

Methods

Study design and patients

We analysed HRM data from a large cohort of patients referred for investigation of oesophageal symptoms who completed ten SWS and a standardised STM (development set). We then tested the validity of these findings in a separate cohort at a second centre (validation set). The development study enrolled consecutive patients referred for oesophageal HRM at Nottingham University Hospitals (Nottingham, UK) between Jan 1, 2010, and Dec 31, 2013. The validation study enrolled consecutive patients referred to University Hospital Zürich (Zürich, Switzerland) between April 1, 2013, and May 31, 2015. Demographic data, clinical symptoms, endoscopy findings, current medication, previous medical history and prior surgeries were recorded. Consent was obtained from all patients prior to HRM studies. The analysis of patient data was approved by Zürich University ethics committee (KEK-ZH-Nr. 2013-0176, 2014-0013).

See Online for appendix

Patients were grouped by predominant symptom (ie, main indication for investigation): group 1 included patients with dysphagia, group 2 included patients with suspected reflux symptoms including heartburn, acid regurgitation, and non-cardiac chest pain (without dysphagia), and group 3, which was studied in the development set only, included patients with dyspepsia and other non-oesophageal symptoms. Individuals with pharyngeal dysphagia and patients who did not complete the study were excluded.

Procedures

All patients were studied after fasting for a minimum of 4 h. HRM was done in the upright, seated position by use of a 36-channel solid-state catheter (Manoscan 360, Sierra Scientific Instruments, Given Imaging, CA, USA). Before they started the study, participants were instructed to report symptoms that occurred during the procedure.

After a 5 min adaptation period, baseline measurements of oesophagogastric junction morphology and pressure were obtained. Ten 5 mL SWS were given to the patient via a syringe in the upright position. SWS were followed by a standardised 200 g STM. Patients were instructed to eat and drink as normal (water was provided if patients had swallowing difficulties) and the time taken to complete the STM (censored at 8 min) and the weight of any food not ingested were recorded. The STM consisted of either a cheese and onion pasty (Ginsters, Callington, UK) in the Nottingham studies and soft-cooked long-grain rice (Uncle Bens, Brussels, Belgium) in the Zürich studies. During the validation of this method, results from the two STMs were compared and found to be almost identical.[18,22]

Proprietary software was used to analyse HRM data (Manoview version 3.0.1) as described previously.[18,19] A summary of the diagnostic criteria used to classify motility disorders via SWS (CCv3) and via STM (CC-S) is provided in the appendix (p 8). The key differences were the upper limit of normal for integrated relaxation pressure (15 mm Hg in CCv3 *vs* 25 mm Hg in CC-S) and diagnosis of ineffective motility disorder (ie, >50% effective contractions in CCv3 *vs* >20% effective contractions in CC-S).[23] Consistent with CCv3, only abnormalities that occurred more than once were classified as a motility disorder. The established diagnostic hierarchy was applied in CC-S. Major motility disorders included achalasia (≥2 obstructive and ≤1 effective contractions), oesophagogastric junction outlet obstruction (≥2 obstructive and >1 effective contractions); spasm (≥2 spastic contractions); hypercontractile oesophagus (ie, jackhammer oesophagus; ≥2 hypercontractile contractions); and absent peristalsis (<1 effective swallow). Minor motility disorders included hypertensive oesophagus (ie, nutcracker oesophagus ≥2 hypertensive contractions) and ineffective motility (≥80% failed or ineffective contractions; additionally, patients with ≥2 runs of ≥5 ineffective contractions were noted). Remaining individuals were normal (appendix p 1).

Symptoms were assessed in the development set. Only symptoms reported by patients during HRM studies and documented in the contemporaneous HRM report were considered. Symptom-associated dysfunction was defined as the occurrence of typical symptom events within 10 s or less after abnormal motility during the HRM study.[18] The short time window ensures high face-validity for this method. This analysis investigated whether STM reproduced typical patient symptoms and whether the likelihood of reporting symptoms was higher in patients with oesophageal motility disorders than in those with normal motility.

Statistical analyses

We did not calculate statistical power because the prevalence of motility disorders is unknown. A large case series was considered necessary to ensure that individuals with all major motility disorders were included in the analysis.

We did the statistical analyses using SPSS 18.0 package for Windows. We used descriptive statistics to characterise demographic and manometric findings. Parametric data are reported as mean (SD). We made comparisons with Student's *t* test for continuous data and χ^2 analysis (for cell size >5) or Fisher's exact test (for cell size <5) for categorical data. We used Cohen's κ statistics to evaluate the agreement between the diagnosis established by SWS and STM. The strength of agreement was defined as poor if it was less than 0·20, fair if 0·21–0·40, moderate if 0·41–0·60, good if 0·61–0·80, and very good 0·81–1·00.[24] We considered a p value less than 0·05 to be statistically significant. These studies are registered with ClinicalTrials.gov, numbers NCT02407938 and NCT02397616.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

815 consecutive patients were referred for HRM studies at Nottingham University Hospitals during the development study period. 38 (5%) individuals with pharyngeal dysphagia and 27 (3%) patients who did not receive STM were excluded. Data from 750 (92% of total; 330 male and 430 females patients; mean age 52·5 years [SD 16·9], median age 53 years [range 18–90]) patients were analysed grouped by predominant symptom: group 1 contained 360 patients with oesophageal dysphagia, group 2 contained 329 patients with suspected reflux symptoms, and group 3 contained 61 patients with dyspepsia and other non-oesophageal symptoms. Demographic and clinical data are shown in table 1. 221 (75%) of 295 consecutive patients referred for HRM studies at University Hospital Zürich met inclusion criteria for the validation study (appendix p 9). In the validation set, 98 patients had oesophageal dysphagia (group 1) and 123 patients had suspected reflux symptoms (group 2). There were no significant differences between the demographic and clinical data of patients recruited in the development set (table 1) and validation set (appendix p 9), except for the number of patients with a history of upper gastrointestinal surgery, which was reported by 109 (15%) patients in the development set and five (2%) patients in the validation set (p<0·0001).

Overall, the proportion of patients with a major motility disorder diagnosed with CCv3 on the basis of SWS was similar between the development (163 [22%] of 750 patients) and validation (49 [22%] of 221 patients) sets (p=0·84). In both studies, more patients were diagnosed with major motility disorders during STM than during SWS (development set: 321 [43%] patients with STM *vs* 163 [22%] patients with SWS, p<0·0001; validation set: 73 [33%] patients *vs* 49 [22%], p=0·014; table 1; appendix p 9).

The inclusion of the STM in HRM studies led to a new diagnosis of a major oesophageal motility disorder in 168 (22%) of 750 patients in the development set, of whom 86 had minor dysmotility and 82 had normal

	Group 1 (dysphagia; n=360)	Group 2 (reflux symptoms; n=329)	Group 3 (other symptoms; n=61)	Total (n=750)
Sex				
Men	161 (45%)	146 (44%)	23 (37%)	330 (44%)
Women	199 (55%)	183 (56%)	38 (62%)	420 (56%)
Age (years)	53·5 (18·4)	51·3 (14·4)	52·7 (17·4)	52·5 (16·9)
Prior surgery				
Achalasia surgery	21 (6%)	3 (1%)	2 (3%)	26 (3%)
Post-fundoplication	41 (11%)	33 (10%)	7 (11%)	81 (11%)
Post-bariatric	1 (<1%)	0	1 (2%)	2 (<1%)
Any dysmotility				
SWS	259 (72%)	199 (60%)	40 (66%)	498 (66%)*
STM	292 (81%)	148 (45%)	33 (54%)	473 (63%)
Major dysmotility				
SWS	125 (35%)	32 (10%)	6 (10%)	163 (22%)†
STM	241 (67%)	64 (19%)	16 (26%)	321 (43%)
Minor dysmotility				
SWS	134 (37%)	167 (51%)	34 (56%)	335 (45%)†
STM	51 (14%)	84 (26%)	17 (28%)	152 (20%)

Data are n (%) or mean (SD). Overall, the diagnostic yield of major motility disorders in the whole group was increased by STM compared to SWS (p<0·0001). HRM=high-resolution manometry. SWS=single water swallows. STM=solid test meal. *p=0·19 for comparison of prevalence between SWS and STM. †p<0·0001 for comparison of prevalence between STM and SWS.

Table 1: **Demographic parameters and HRM diagnoses in the development study**

		Diagnosis on STM								
		Achalasia	Oesophagogastric junction outflow obstruction	Spasm	Hypercontactile oesophagus	Absent	Ineffective oesophageal motility	Hypertensive oesophagus	Normal	Total
Diagnosis on SWS	Achalasia	41	2	0	0	0	0	0	0	43
	Oesophagogastric junction outflow obstruction	0	33	0	0	0	0	0	0	33
	Spasm	1	8	19	0	0	0	0	0	28
	Hypercontactile oesophagus	0	0	1	2	0	0	0	0	3
	Absent	2	26	2	0	16	10	0	0	56
	Ineffective oesophageal motility	0	57	15	0	0	108	1	126	307
	Hypertensive oesophagus	0	7	6	1	0	0	12	2	28
	Normal	0	53	27	2	0	14	7	149	252
	Total	44	186	70	5	16	132	20	277	750

***Figure 1*: Diagnostic agreement between SWS and STM in the development set**
Purple shading shows patients who had minor motility disorders or normal motility on HRM with SWS but major motility disorder on STM. Green shading shows patients with major motility disorder on HRM with SWS but minor motility disorder or normal motility on STM. Blue shading shows patients with minor motility disorder or normal motility on both SWS and STM. Bold lines show the division between major and minor motility disorders. SWS=single water swallows. STM=solid test meal. HRM=high-resolution manometry.

findings on SWS (purple shading on figure 1). Another 40 (5%) patients with major dysmotility had their diagnoses reclassified to a form of major dysmotility that was higher in the diagnostic hierarchy (eg, spasm reclassified as achalasia). 37 (17%) of 221 patients in the validation set, of whom ten had minor dysmotility and 27 had normal findings on SWS, were reclassified with a major motility disorder on STM (appendix p 2). Similarly, another eight (4%) patients in the validation set with one form of major motility disorder were reclassified to another major motility disorder with STM. In both studies, the prevalence of any oesophageal motility disorder was higher in group 1 patients with dysphagia than in group 2 patients with suspected reflux symptoms (table 1; appendix p 9). This observation was true for diagnoses based on SWS (259 [72%] group 1 patients *vs* 199 [60%] group 2 patients; p=0·0016) and STM (292 [81%] group 1 patients *vs* 148 [45%] group 2 patients; p<0·0001) in the development study, with similar results for the validation study (appendix p 9).

In the development set, group 1 patients with dysphagia were more likely to have a major motility disorder diagnosed on STM (241 [67%] of 360 patients) than on SWS (125 [35%] patients; p<0·0001; table 1). Similarly, in the validation set, more group 1 patients were diagnosed with major motility disorder on STM (50 [51%] of 98 patients) than on SWS (34 [35%] patients; p=0·030; appendix p 9).

In the development set, group 2 patients with suspected reflux symptoms were more likely to have a major motility disorder diagnosed on STM (64 [19%] of 329 patients) than on SWS (32 [10%] patients; p=0·00060). Findings were similar in group 3 patients. In the validation set, the difference between the number of group 2 patients diagnosed with a major motility disorder during STM (23 [19%] of 123 patients) and during SWS (15 [12%] patients) was not significant (p=0·22).

Overall agreement between SWS and STM diagnosis for patients with predominant dysphagia was deemed to be fair in both the development set (κ=0·371, p<0·0001) and validation set (κ=0·330, p<0·0001, respectively). The most common diagnosis established during the STM that was not observed with SWS was oesophagogastric junction outlet obstruction (figure 2; appendix pp 10–11). This finding was particularly prevalent in the 63 group 1 patients with a history of anti-reflux (42 patients) and bariatric procedures (one patient). The fact that more patients had undergone previous upper gastrointestinal surgery in the development set (109 [15%] of 750 patients) than in the validation set (five [2%] of 221 patients) explains, in large part, the 10% difference in the diagnostic yield of major motility disorders with STM between the two studies (43% in development *vs* 33% in validation).

In patients with predominant reflux symptoms, overall agreement between SWS and STM was fair in the development set (κ=0·312, p<0·0001) and poor in the validation set (κ=0·154, p=0·0030). Diagnoses were discrepant in 151 (46%) of 329 patients in the development set and 70 (57%) of 123 patients in the validation set (appendix pp 11–12). The most common change in diagnosis in group 2 patients was from ineffective oesophageal motility based on SWS to normal findings based on STM (figure 2; appendix p 11). Findings were similar for group 3 patients in the development set (appendix p 13).

All major motility disorders, except absent peristalsis, were more common with STM than with SWS. Representative examples of HRM data are shown in the appendix for oesophageal spasm (appendix p 5) and hypercontractile oesophagus (appendix p 6) diagnosed on HRM with STM in patients with normal findings with SWS.

In the development set, typical symptoms were reproduced in nine (1%) of 750 patients with SWS and 461 (61%) patients by STM (p<0·0001; table 2). Patients with dysphagia in group 1 were more likely to report symptoms during the STM than were group 2 or 3 patients (281 of [78%] 360 patients *vs* 180 [46%] of 390 patients; p<0·0001; appendix, p 14).

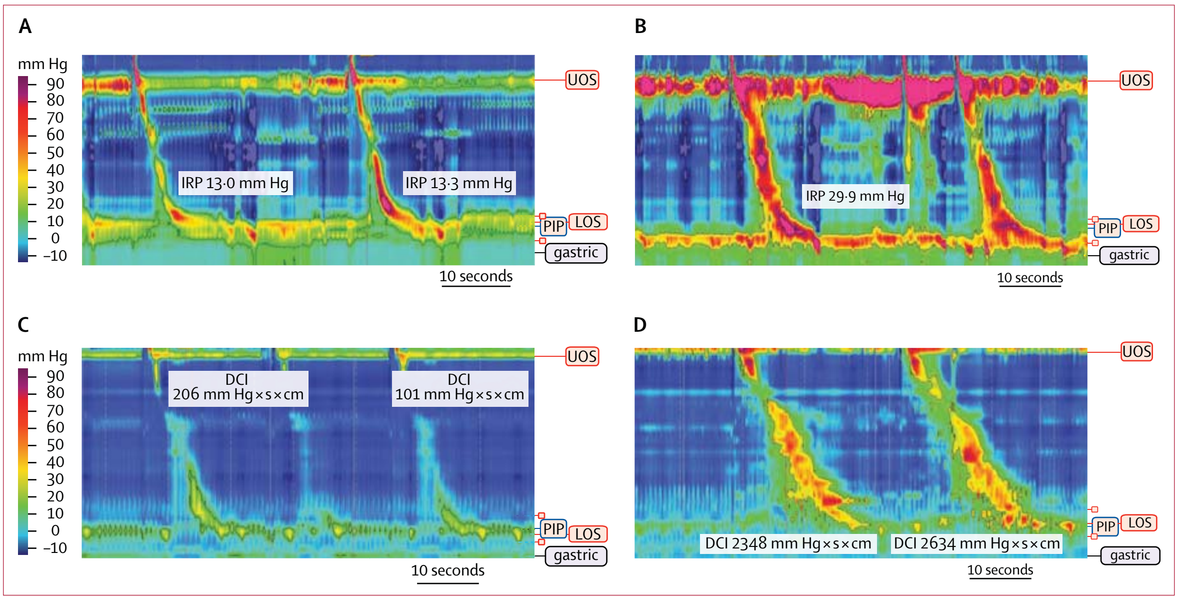

Figure 2: **Examples HRM studies including an STM**
Two representative cases (more detail available in appendix p 3 and 4) showing the impact of including a STM in HRM studies. The upper panel shows (A) normal oesophageal contractility and oesophagogastric junction function with SWS (IRP 13 mm Hg) and, (B) in the same patient, oesophagogastric junction outflow obstruction with IRP of 30 mm Hg during STM. Typical symptoms of dysphagia were associated with compartmentalised pressurisation IRP >50 mm Hg. The lower panel shows (C) ineffective or hypotensive oesophageal motility with SWS and, (D) in the same patient, essentially normal oesophageal motility with effective clearance during STM, indicating preserved physiological reserve. Symptoms did not occur during the HRM study. HRM=high-resolution manometry. STM=solid test meal. SWS=single water swallows. IRP=integrated relaxation pressure. UOS=upper oesophageal sphincter. LOS=lower oesophageal sphincter. PIP=pressure inversion point. DCI=distal contractile integral.

Overall, as classified by CC-S, patients with a major dysmotility disorder were more likely to report symptoms during the STM (265 [83%] of 321 patients) than were those with minor motility disorders (107 [70%] of 152 patients; p=0·0038) or normal motility (89 [32%] of 277 patients; p<0·0001; table 2). The risk of symptoms was similar for major and minor motility disorders in group 1 patients with dysphagia (205 [85%] of 241 patients with major motility disorders *vs* 40 [83%] of 48 patients with minor motility disorders) and was somewhat lower for both major and minor disorders in group 2 and 3 patients (60 [75%] of 80 patients with major motility disorder *vs* 67 [60%] of 111 patients with minor motility disorders; appendix p 14).

	Patients with symptoms during STM	Patients with no symptoms during STM
Major motility disorder on STM*†		
Achalasia	31 (70%)	13 (30%)
Oesophagogastric junction outlet obstruction	163 (88%)	23 (12%)
Aperistalsis	14 (88%)	2 (13%)
Spasm	53 (76%)	17 (24%)
Hypercontractile oesophagus	4 (80%)	1 (20%)
Total	265 (83%)	56 (17%)
Minor motility disorder on STM†		
Hypertensive oesophagus	13 (65%)	7 (35%)
Ineffective oesophageal motility	94 (71%)	38 (29%)
Total	107 (70%)	45 (30%)
Normal motility on STM		
Total	89 (32%)	188 (68%)

Data are n or n (%). All patient groups were combined for this analysis. STM=solid test meal. *p=0·0038 for comparison of major with minor dysmotility. †p<0·0001 for comparison of major dysmotility and minor dysmotility from normal.

Table 2: **Likelihood of symptoms occurring during STM in the development set**

Discussion

Use of HRM has improved the accuracy and diagnostic yield of clinical investigation in patients with suspected oesophageal motility disorders;[25–27] however, our results show that HRM findings based on SWS alone often fail to provide a definitive diagnosis that is capable of explaining the cause of oesophageal symptoms.

We report the findings of two cohort studies that compared the diagnostic yield of clinically relevant motility disorders using a novel HRM protocol that was validated in an accompanying Article.[22] The inclusion of an STM in the HRM protocol increased diagnostic yield in both the development and validation studies. The effect of the inclusion of an STM in the HRM protocol was most marked in patients with dysphagia; however, an effect was also seen in patients referred for investigation for suspected reflux symptoms. These findings are consistent with the results of pilot studies that used HRM with an STM (in this case a pasty, as used in the development set) reported by Sweis and colleagues[19] and results of studies with conventional manometry systems, as reported by Blonski and colleagues[11] and Allen and colleagues,[14] who observed a higher incidence of motor abnormalities with food ingestion compared with water swallows. Our findings differ from those of Xiao and colleagues[21] who did not find a significant increase in clinically relevant motility disorders with the inclusion of viscous or solid swallows. This negative finding is probably caused by the small number of swallows (two viscous swallows and two solid dry crackers) evaluated by the investigators. Even in healthy individuals, oesophageal motility is variable during STM, with between 20% and 100% of pharyngeal swallows accompanied by effective oesophageal contractions.[22] In patients reporting oesophageal symptoms, the likelihood of detecting a major motility disorder and inducing oesophageal symptoms increases after the first minute of a 200 g STM that requires 3–8 min to complete. Evidence presented in the accompanying paper that 30 pharyngeal swallows are needed to obtain a representative sample of oesophageal motility during STM ingestion.[22]

The disorder detected during STM that was most often not observed with the standard SWS protocol was oesophagogastric junction outlet obstruction. About 20% of patients in the development set and 8% of patients in the validation set received a new diagnosis of outlet obstruction with STM. The clinical relevance of this finding was supported by concurrent reports of symptoms with oesophageal pressurisation by nearly 90% of patients with this CC-S diagnosis (table 2). Increased diagnostic yield for outlet obstruction resulting from a physiological challenge has also been reported by Xiao and colleagues when they used viscous liquid and marshmallow swallows.[17] This heterogeneous disorder can be related to structural pathology (eg, peptic stricture) or an incomplete achalasia syndrome.[28] Further assessment, ideally by endoscopic ultrasound, is indicated because submucosal or extra-luminal malignancy (ie, pseudoachalasia) or other clinically relevant pathologies are found in at least 15% of patients with this disorder.[29] Additionally, the presence of a circumferentially thickened wall (>4 mm) in the distal oesophagus is characteristic of achalasia, spasm, and related disorders.[29,30] In a prospective study of patients with symptoms after fundoplication surgery but normal endoscopy and radiology findings,[20] STM improved the yield for oesophagogastric junction outlet obstruction from four (7%) of 57 patients with SWS to 15 (26%) patients with STM. Pneumatic dilatation produced good results in seven (58%) of 12 post-fundoplication patients with outlet obstruction with no serious complications.[20] The remainder needed surgical revision. Similar findings have also been independently reported in patients with symptoms after bariatric surgery (appendix p 7).[31]

The diagnostic yield of other major motility disorders was also increased by inclusion of an STM in HRM studies (figure 1; appendix p 2). This increased yield included five patients with achalasia and pan-oesophageal pressurisation, whose integrated relaxation pressure was less than 15 mm Hg during SWS but greater than 25 mm Hg during the STM. Several additional cases of oesophageal spasm and hypercontractile motility (appendix p 5–6) were also detected by use of this method and up to 80% of these individuals reported symptoms during the STM study (table 2). Conversely, other patients with oesophageal spasm or absent motility during SWS appeared to have improved function during the STM, receiving a diagnosis of either ineffective, or even normal, oesophageal motility (figure 1; appendix p 2). In contrast to patients with spasm during STM, most individuals with oesophageal spasm detected only during SWS had no symptoms during the physiological challenge. A plausible explanation is that oesophageal contractions are slower (longer distal latency), more vigorous (higher distal contractile integral), and better coordinated (smaller gaps in the contractile front) with solid swallows than with water swallows.[19,32] This result is consistent with the findings of Tutuian and colleagues in their studies of patients with oesophageal spasm using combined impedance-manometry.[33]

The HRM method used also affected the diagnosis of minor motility disorders. Many patients with ineffective or fragmented oesophageal motility with SWS had normal motility during STM, indicating the presence of physiological reserve. This finding resulted from two factors: first, the effects of solid bolus swallows on oesophageal contractility already described and, second, the different thresholds for ineffective or fragmented motility applied by CCv3 based on SWS (<50% effective contractions[6]) and CC-S with solids (<20% effective contractions[22]). The CCv3 threshold for ineffective oesophageal motility was selected on the basis of results from physiological studies that show hypotensive contractions (distal contractile integral <450 mm Hg) and large gaps (>5 cm) in the contractile front to be associated with incomplete bolus transport;[34,35] however, the association of these findings with symptoms is weak and the clinical relevance of this diagnosis has been questioned.[21,34,36] In the accompanying Article,[22] the 95% threshold for diagnosis of ineffective oesophageal motility was consistent for SWS and STM studies (>20% effective contractions). Moreover, the likelihood of a patient reporting symptoms during STM was higher in patients with 20% or fewer effective oesophageal contractions than in those with normal motility defined by this threshold (71% *vs* 32%; p<0·0001). On this basis, we propose that the current diagnostic classification (CCv3) lacks specificity for ineffective oesophageal motility and that this diagnosis should be restricted to patients with clinically relevant dysfunction with less than 20% effective oesophageal contractions during SWS or STM.

Our findings also suggest that the removal of the minor motility disorder hypertensive oesophagus from CCv3 might have been premature. First, this finding was found in fewer than 5% healthy controls.[22] Second, half (14 of 28) of patients with hypertensive oesophagus on SWS had either oesophagogastric junction outlet obstruction, oesophageal spasm, or hypercontractile swallows during STM (conversely, only two [7%] of 28 patients had normal motility on STM). Third, nearly two-thirds of patients with hypertensive oesophagus had typical symptoms during the STM. These findings are consistent with results from a clinical outcome study showing that patients with hypertensive oesophagus had a relatively high risk of persistent symptoms compared with other patients with minor motility disorders.[36] Together, these findings provide a strong case for the reinstatement of hypertensive oesophagus in the diagnostic classification of oesophageal motility disorders.

Symptoms were reproduced more often with STM (61%) than with SWS (1%) in our development cohort. The likelihood of symptoms being reproduced was higher in patients with major motility disorders than in patients with minor motility disorders defined via CC-S (83% *vs* 70%, p=0·0038) and in patients with normal HRM findings (32%, p<0·0001 *vs* patients with motility disorders). This stepwise decrease with major, minor, and normal motility is probably because the likelihood of symptoms is more closely related to impaired bolus transport than abnormal motility per se.[8,9,37] The use of high-resolution impedance manometry (HRIM) that combines motility studies with bolus transport offers an improved diagnostic evaluation tool in patients with dysphagia. In the future, HRIM will help to clarify the mechanism of symptoms and disease during STM studies.[38,39] Reports of symptoms in about one in three patients with normal motility will be a so-called nocebo effect in some cases. In others, symptoms occurred after a series of three to four failed or ineffective oesophageal contractions, which is defined as normal motility by the CC-S; however, individuals with visceral hypersensitivity report oesophageal sensations at relatively low stimulus intensity.[40–44] Determining the interaction between biophysical and psychogenic factors in the generation of functional oesophageal symptoms is beyond the scope of this study, but a key aim of ongoing research.

One limitation of this clinical study is that all measurements were acquired in the upright, seated position, and not the supine position used in most previous studies. Oesophageal motility is affected by position.[17,20] However, differences in HRM measurements are generally small and rarely change the diagnosis from a minor to a major motility disorder.[17,20] The accompanying Article provides reference values from 72 healthy age-and-sex stratified volunteers for SWS and STM in the upright position.[22] We also note that this study used the ManoScan 360 system and that the threshold values for pressure measurements are specific to this equipment. Another issue that requires comment is that the increase in diagnostic yield of major motility disorders was higher in the development set than in the validation set. This difference was not due to the choice of test meals because HRM data from the pasty and rice meals were essentially the same.[22] Rather, the difference is most likely because of the relatively high number of patients with persistent symptoms related to oesophagogastric junction outlet obstruction after fundoplication or bariatric surgery who were referred to hospital in Nottingham compared with Zürich (15% *vs* 2%). These patients were not excluded because the biophysical principles that underpin the CCv3 are still applicable to these patients and provide clinically relevant information.[20,31,45] We acknowledge the lack of outcome data in our study. Future studies will assess agreement between HRM with STM and measurements by other techniques, including the endoscopic functional lumen imaging probe. This device provides direct evidence of oesophagogastric junction distensibility and abnormal oesophageal contractility in patients with achalasia and related conditions in whom routine HRM with SWS were not diagnostic.[46,47] Potential advantages of HRM with STM compared with this new technology include minimal cost, safety, ease of use under physiological conditions (ie, non-sedated patients eating and drinking in the upright position), and the ability to associate abnormal findings with patient symptoms.

Our results support the hypothesis that the inclusion of an STM in HRM studies increases the diagnostic yield for the detection of major motility disorders. The clinical relevance of these new diagnoses was supported by the temporal association between abnormal motility and patient symptoms in more than 80% of patients with a major motility disorder during the physiological challenge. Conversely, many individuals with ineffective oesophageal motility on SWS had normal motility and no difficulty in completing the meal. These findings provide strong evidence that the inclusion of an STM in HRM studies can increase both diagnostic sensitivity and specificity for clinically relevant, symptomatic motility disorders.

Contributors

MF, BM, and RS developed the study concept and design. MH, BM, KK, JW, ET, and MF acquired the clinical data. DA, BM, MH, and MF did the data analysis and data interpretation. All authors critically appraised and approved the manuscript.

Declaration of interests

We declare no competing interests.

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