Achalasia diagnosed despite normal integrated relaxation pressure responds favorably to therapy

Short Title: Therapeutic response in normal IRP achalasia

Santosh Sanagapalli, Sabine Roman, Audrey Hastier, Rupert Leong, Kalp Patel, Amanda Raeburn, Matthew Banks, Rehan Haidry, Laurence Lovat, David Graham, Sarmed Sami, Rami Sweis

GI Physiology Unit, University College London Hospital, 235 Euston Rd London, United Kingdom NW1 2BU

Corresponding author:

Dr. S. Sanagapalli

Department of Gastroenterology

St. Vincent's Hospital Sydney

390 Victoria St, Darlinghurst NSW, Australia

E: Santosh.sanagapalli@svha.org.au

Tel: +61283821111

Abstract

Background

Achalasia diagnosis requires elevated integrated relaxation pressure (IRP; manometric marker of lower esophageal sphincter (LES) relaxation). Yet some patients exhibit clinical features of achalasia despite normal IRP; and have LES dysfunction demonstrable by other means. We hypothesized these patients to exhibit equivalent therapeutic response compared to standard achalasia patients.

Methods

Symptomatic achalasia-like cases, despite normal IRP, displayed evidence of impaired LES relaxation using rapid drink challenge (RDC), solid swallows during high-resolution manometry, and/or barium esophagogram; were treated with achalasia therapies and compared to standard achalasia patients with raised IRP. Outcomes included equivalence for short- and long-term symptom response and stasis on barium esophagogram.

Key Results

29 normal IRP achalasia cases (14 males, median age 50y, median Eckardt 6, barium stasis 12±7cm) and 29 consecutive standard achalasia controls underwent therapy. Amongst cases, LES dysfunction was most often identified by RDC and/or barium esophagogram. Short-term symptomatic success was equivalent in cases vs. controls (90% vs. 93%; 95% CI for difference: -19% to 13%). Median short-term (1 vs. 1; 95% CI for difference: 0-1) and long-term Eckardt scores (2 vs. 1; 95% CI for difference: 0-2) were similar in cases and

controls respectively. Adequate clearance was observed in 67% of cases vs. 81% of controls on post-therapy esophagogram.

Conclusions & Inferences

We described a subset of achalasia patients with normal IRP, but impaired LES relaxation identifiable only on additional provocative tests. These patients benefited from treatment, suggesting that such tests should be performed to increase the number of clinically relevant diagnoses.

Key Points

- In some patients with clinical features of achalasia, impaired LES relaxation is only demonstrable using additional provocative test(s) (free drinking and solid swallows during manometry, barium esophagogram), and not with standard manometric testing. Clinical relevance of such diagnoses is uncertain.
- A cohort of such patients were treated with achalasia therapy and exhibited a favorable response, equivalent to achalasia diagnosed in the conventional fashion
- Additional provocative tests should be added to standard manometric testing to ensure optimum sensitivity of achalasia diagnosis

Introduction

Achalasia is an esophageal motility disorder characterized by the absence of normal peristalsis and failure of adequate deglutitive relaxation of the lower esophageal sphincter (LES). Timely diagnosis of the condition and differentiation from other mechanical and functional causes of dysphagia permits the use of achalasia-specific therapies that target the non-relaxing LES, thereby usually leading to a rapid and significant reduction in symptom burden.[1,2] Further, cases of disease relapse over time are observed with all treatment modalities; therefore, it is equally important to identify relapsed achalasia patients who would benefit from retreatment.

Initial investigation of dysphagia and other esophageal symptoms usually involves endoscopy and/or barium esophagogram, and in typical cases of achalasia both tests demonstrate characteristic signs. However, neither test has sufficient sensitivity or specificity to definitively diagnose or exclude achalasia, especially in early stages of the disease.[3,4] In the last decade, high-resolution manometry (HRM) has emerged as a valuable tool to aid in the diagnosis of achalasia and other esophageal motor disorders. With superior diagnostic accuracy, reproducibility and inter-observer consistency, HRM has superseded conventional manometry systems as the gold standard for the diagnosis or exclusion of achalasia.

According to the criteria described in the Chicago Classification for esophageal motility disorders, essential to the diagnosis of achalasia is the presence of a raised integrated relaxation pressure (IRP; a surrogate marker of LES relaxation on

HRM).[5] This metric is calculated following administration of 5mL water swallows. Yet it is self-evident that this pattern of administration does not replicate normal swallowing behavior. By also administering solid swallows or higher volumes of water (rapid drink challenge, RDC; where 200mL of water is drunk freely), esophageal physiology can be analyzed whilst reproducing normal eating and drinking behaviour. It has become increasingly clear that the addition of such adjunctive swallowing challenges to the standard HRM protocol is not only valid and reproducible, but improves the diagnostic accuracy of HRM,[6-9] and is increasingly used worldwide.[10] Specifically in achalasia, the addition of solid swallows and RDC to the HRM protocol can help identify subtle impairment of esophago-gastric junction (EGJ) relaxation and resistance to flow that would have otherwise been missed with standard 5mL water swallows alone.[11,12] Other, newer and advanced technologies including the functional lumen imaging probe (FLIP) by measuring EGJ distensibility[13] and high resolution impedance manometry by calculating bolus flow time,[14] as well as simpler tools such as the barium esophagogram,[15] have also been utilized to identify similar cases of achalasia despite normal IRP. Yet, it is important to establish the clinical relevance of such extra diagnoses thereby obtained. One method to do so would be to demonstrate good outcomes following therapy in such patients.

We observed a similar cohort of patients who exhibit all the symptomatic hallmarks of achalasia but who might not ordinarily be offered EGJ-disrupting therapy as the standard 5mL water swallow IRP is found to be normal and, in turn, presumed to be non-obstructive. Our aims were twofold. Firstly, to establish that inadequate deglutitive LES relaxation is demonstrable in these patients through

the use of additional provocative testing during manometry or barium studies, and without the use of any advanced technologies. Secondly, to establish the clinical relevance of these extra positive diagnoses, by describing therapeutic outcomes. To achieve these, we compared the diagnosis and response to therapy of such "normal IRP achalasia" patients with another group of patients with achalasia and standard raised IRP.

Materials and methods

Patients and study design

We performed a retrospective cohort study based on prospectively collected data of subjects eligible for inclusion presenting to either of two tertiary referral centers (University College London Hospital, United Kingdom and Édouard-Herriot Hospital, Lyon, France) between 2013 and 2017. Patients who presented primarily with dysphagia had endoscopy to exclude structural pathology before proceeding to HRM with ten standard 5mL water swallows. Patients underwent additional provocative testing when HRM with standard water swallows demonstrated an absence of normal peristalsis and a median IRP of <15mmHg (i.e. not fulfilling the Chicago Classification criteria for diagnosis of achalasia).[5] For each center, routine additional provocative testing comprised of:

- UK: Patients had attempted administration of RDC with 200ml water drunk freely, as well as five single solid swallows where tolerated. They also had assessment with timed barium esophagogram (TBE).
- France: Patients underwent RDC and conventional barium esophagogram.

Symptoms were assessed at baseline and following therapy for all patients using the Eckardt score. Patients who exhibited an Eckardt score >3 were included in the study when one or more of the additional tests demonstrated evidence of a non-relaxing LES, as defined below in italics (normal IRP achalasia group). The presence of any other major motility disorder based on Chicago Classification criteria, or any history of esophagogastric surgery for indications other than achalasia were exclusion criteria. Inclusion of patients both with and without a past diagnosis and/or treatment of achalasia was permitted (Figure 1).

An equal number of consecutive subjects who did exhibit a raised median IRP >15mmHg with 5mL water swallows and had a definitive diagnosis of achalasia without the need for additional provocative testing were included as the standard achalasia control group. These control subjects otherwise fulfilled all the other inclusion and exclusion criteria described above (Figure 1).

Both groups of subjects were offered treatment with standard achalasia therapies as per standard practice, at the discretion of the patient and treating physician; botulinum toxin injection, pneumatic dilation, per-oral endoscopic myotomy (POEM) and/or Heller myotomy. Pneumatic dilation was performed using a graded distension protocol as previously described by Boeckxstaens et al.[1] Briefly, an initial 30mm dilation was followed by a 35mm dilation within 4 weeks. Subjects with inadequate response (Eckardt score >3) were treated with an additional 40mm dilation. In the UK cohort, esophageal emptying was assessed at baseline and following therapy using the TBE.

High-resolution manometry

All subjects at the French site, and those presenting to the UK site after May 2016 had studies performed using a 36-channel solid-state HRM system (Manoscan Eso Z, Medtronic, Hertfordshire, UK). Prior to May 2016, HRM at the UK site was performed using a 20-channel water perfused manometry system as previously described (Solar GI HRM, Medical Measurement Systems, Enschede, The Netherlands).[9] A standard HRM protocol was initially performed, whereby ten 5mL water swallows were administered 30s apart.

Using the criteria detailed in the Chicago Classification for esophageal motility disorders version 3.0, following 5mL water swallows, all standard parameters were measured including the IRP.[5] While upper limit of normal for IRP is slightly higher for water-perfused HRM systems,[16] the 15mmHg cutoff was used to define all normal IRP achalasia patients for standardization purposes, and considering that in any case this would be more rather than less strict in defining patients with a non-raised IRP. Furthermore all control subjects had IRP well above the upper limit of normal for either system. Both normal IRP achalasia and standard achalasia control subjects were subtyped into three groups (Type I, II and III) based on esophageal body contractility findings with 5mL water swallows, according to the conventional criteria.[5]

Additional provocative testing on HRM

Where the RDC test was performed, the patient drank 200mL of water through a straw within 30s and without taking a break. Where solid swallows were assessed, five bread swallows (1cm^3 cubes of buttered white bread) were administered, with 30s in between each bread swallow.[9] *For solid swallows and RDC the presence of pan-esophageal pressurization, defined as uniform pressurization of ≥30 mmHg extending from the UES to the EGJ, was taken to indicate a non-relaxing LES*.[5]

Barium Esophagogram

In the UK cohort, TBE was performed prior to and following therapy according to a standardized protocol.[17] *On TBE, a non-relaxing LES was inferred by the persistence of at least a 5cm residual barium column at 5 minutes*. *For subjects who were assessed with conventional barium esophagogram in France, non-relaxing LES was defined when there was evidence of holdup of contrast flow through the EGJ that persisted up to 5 minutes*.

Outcomes

The primary outcome was the number of patients with adequate treatment response, defined as Eckardt score of ≤3 at three months post-therapy. Secondary outcomes included quantitative Eckardt score at 3 months post-therapy, both binary and quantitative long-term symptom outcomes, and barium column stasis at 5 minutes on post-therapy where TBE was undertaken. Sub-analyses of

manometric data and treatment outcomes by HRM system type, by study location (UK vs. France), and between treatment-naïve and experienced subjects were performed.

Statistical Analysis

An equivalence analysis of treatment outcomes was undertaken between the two study groups, given that expanding EGJ-disrupting achalasia therapy to the normal IRP achalasia group provides access to treatments that are well established and consistently effective in standard achalasia patients.[1] A minimum clinically meaningful difference between groups in the primary outcome of 20% was pre-specified, considering that even a 20% lower efficacy rate clearly represents vast superiority over the negligible response rates to sham and placebo therapies previously demonstrated in achalasia.[18] A minimum of 28 subjects in each arm achieved 80% power to detect an equivalence margin difference between the groups for the primary outcome of 20%, estimating that the primary outcome in the control group to be achieved in 90% of subjects[1] and aiming to show that the treatment was equally effective in both groups. The null hypothesis was that treatment response in normal IRP achalasia is not equivalent to controls. The unpooled two-sided Z test was used with statistical significance defined as <0.05.

Pairwise comparisons were performed for categorical characteristics between study groups using a chi-square or Fisher's exact test as appropriate, while continuous symptom and test result covariates were compared using a

Wilcoxon rank sum test or unpaired T test for non-parametric/ordinal and parametric variables respectively. Analysis was conducted using IBM SPSS Statistics for Mac, version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Baseline clinical characteristics

A total of 4975 HRM studies were performed across both sites during the study period. In total 29 subjects met the inclusion criteria for, and thereby comprised, the normal IRP achalasia group (14 male, median age 50 (interquartile range 39-60)). During this same period, 357 cases of standard achalasia with raised IRP were diagnosed.

16 normal IRP achalasia subjects (55%) were newly diagnosed and treatment-naive whereas 13 were treatment-experienced (7 Heller myotomy, 6 pneumatic dilation, 1 Botulinum toxin injection) and had been previously diagnosed with achalasia, with median duration since prior therapy of 8 years (IQR 5-12 years) (Table 1).

When compared to 29 consecutive standard achalasia subjects (control group), Type I was the most common subtype (*N*=16, 55%) in normal IRP achalasia whereas among controls there was predominance of Type II subtype (*N*=20, 69%; *P*=0.02 for comparison). In terms of disease severity at baseline, the control group tended to be more symptomatic than the normal IRP subjects; though the absolute

difference in magnitude of symptoms between the two groups was small (median Eckardt score 7 vs. 6 respectively, *P*=0.01). Mean height of the residual barium column for normal IRP subjects at 5 minutes post ingestion was 12cm ±7cm and this was not significantly different in controls (*P*=0.14). As intended, the median IRP for 5mL water swallows was significantly higher in the standard achalasia control group compared with the normal IRP achalasia group (*P*<0.0001) (Table 1).

Baseline manometric characteristics

As per the inclusion criteria, all normal IRP subjects had a median IRP for ten 5mL water swallows of less than 15mmHg (group median 8mmHg (IQR 4-12)). The LES resting pressure was 14mmHg (IQR 11-18) in normal IRP achalasia subjects in studies performed using the MMS HRM system and 9mmHg (IQR 5-14) in studies using the Medtronic system. In most normal IRP achalasia subjects, resistance to flow across the EGJ was diagnosed by a combination of RDC and barium esophagogram (Table 2 and Figure 2), while solid swallows helped reaffirm the diagnosis defined by RDC and barium esophagogram in some cases (Figure 3). There was no significant difference in the baseline manometric characteristics of the normal IRP subjects when analyzed by study site or HRM system used (Supplementary Tables 1 and 2).

Therapy and outcomes

Primary therapy was by pneumatic dilation or POEM in the majority of both cases and controls, and the type of primary therapy did not differ significantly between

groups (*P*=0.92; Figure 4). The number of subjects with short-term treatment success by Eckardt score (the primary outcome) was 90% (95% CI 77%-96%) in normal IRP achalasia versus 93% (95% CI 81%-98%) in standard achalasia controls. The difference in short-term treatment success rates was -3% (95% CI -19% to 13%; *P* for equivalence = 0.02), i.e. within the specified 20% margin for equivalence. The median short-term post therapy Eckardt score was 1 (IQR 0-2) in normal IRP achalasia and 1 (IQR 0-1) in controls, with 95% CI for difference in short-term Eckardt score of 0 to 1 (Figure 5).

19 normal IRP achalasia subjects and 26 controls had long-term follow up data of 6 months or more. The median duration of long term follow up was 18 months (IQR 13-26 months) in normal IRP achalasia and 16 months (12-24 months) in controls. 84% (95% CI 66%-94%) of normal IRP subjects retained adequate long-term symptoms relief vs. 85% (95% CI 70-%-93%) of controls (95% CI for difference in long term success rates -24% to 20%). The median long-term post therapy Eckardt score was 2 (IQR 1-3) in normal IRP achalasia and 1 (IQR 0-2) in controls, with 95% CI for difference in long-term Eckardt score of 0 to 2.

There was no significant difference in treatment outcomes when comparing treatment naïve and experienced normal IRP patients in terms of short and long-term symptomatic response to achalasia therapy (Supplementary Table 3). Similarly, there was no significant difference in treatment outcomes by study site (Supplementary Table 1).

Of subjects assessed by TBE post-therapy (18 normal IRP achalasia, 21 controls), adequate clearance of barium at 5 minutes was observed in 67% of normal IRP subjects and 81% of controls (95% CI for difference in proportions -39% to 13%). The median barium column height at 5 minutes was 3.95cm in normal IRP cases and 0cm in controls (95% CI for difference 0 to 4.4cm).

In the normal IRP group, all 3 initial treatment failures were in patients who underwent pneumatic dilation. 2 of these subjects were subsequently referred for Heller myotomy and obtained a good treatment response. Of the 8 subjects in this group who had initial treatment success with pneumatic dilation, 2 required a second series of dilations for symptom recurrence within the follow up period while the other six had no subsequent symptom recurrence during the follow up period.

Discussion

We describe a cohort of patients who, despite having a normal IRP for water swallows on HRM, demonstrated resistance to bolus flow across the EGJ detectable via other means; free drinking of water (RDC), solid swallows and/or barium esophagogram. Subsequently, the response of subjects in this cohort to conventional achalasia therapies was equivalent compared to those with achalasia diagnosed according to standard criteria. We found close concordance in results for both short (90% vs. 93%) and long-term (84 vs. 85%) symptomatic success in cases and controls, all supporting our hypothesis that these are also cases of achalasia warranting therapy that are undiagnosed when challenged with water swallows alone.

While there was a significant difference in baseline symptom severity between the groups, with normal IRP subjects slightly less symptomatic, the magnitude of this difference was small (median Eckardt score 6 vs. 7) and all subjects had sufficiently severe symptoms at baseline to warrant therapy. Nevertheless, this finding is compatible with the postulate that these patients exhibit a milder form of the disease. In any case, both normal IRP and standard achalasia subjects responded similarly effectively to therapy, with the 95% confidence interval for the difference between groups in the primary outcome of short-term treatment success being -19% to 13%. Even accepting the most pessimistic end of this interval, this still represents a favorable therapeutic response in the normal IRP group, considering that in the absence of this diagnosis and therapy patients would be left to deal with chronic, potentially progressive symptoms. We did however find a tendency for normal IRP achalasia to have more barium stasis on TBE post-therapy. Based on previous data, this may portend a higher rate of symptom relapse in normal IRP subjects after even longer periods of follow up.[19]

Normal IRP achalasia included both newly diagnosed treatment-naïve patients, as well as patients with symptom relapse after treatment for achalasia at other centers in the past (median duration since prior therapy of 8 years). Therapeutic outcomes were favorable in both. We chose to include experienced patients in addition to naïve since relapse post-therapy is a well-known feature of achalasia, and the same tools with the same normal values are used to define pathology and determine appropriateness for therapy regardless of previous therapeutic

experience. Our data suggest that in either scenario additional provocative testing is more sensitive than reliance on water swallow IRP alone.

In recent times a number of other investigators have also attempted to demonstrate cases of achalasia with normal IRP using varying technologies such as high-resolution impedance manometry,[14] FLIP topography,[13] the barium esophagogram,[15] as well as rapid drink challenge and solid swallows during HRM.[11,12] The present study not only identified normal IRP achalasia patients, but also demonstrated that treatment of such patients with conventional achalasia therapies resulted in good outcomes thus establishing the clinical relevance of the increased diagnostic yield. FLIP in particular has proven useful in a number of applications by measuring the LES distensibility with very high sensitivity and specificity.[13] However, the FLIP technology is expensive and not widely available. The advantage of our approach is that adding a free drinking test or solid swallows to the standard manometry protocol is inexpensive, simple, reproducible and does not require the acquisition of new hardware.

Similarly, the barium esophagogram is a simple and widely available test that is very sensitive at identifying obstruction, being able to identify clinically relevant EGJ dysfunction in cases when IRP is normal.[13] The TBE in particular is helpful in discriminating between those that require therapy from those that might not.[19] Consistent with this, we observed good concordance between positivity on TBE and RDC (Figure 2), though there were a small number of patients with positive TBE and no other positive tests; highlighting again the utility of a protocol such as

the one described using multiple additional provocative tests to maximize the sensitivity of clinically relevant achalasia diagnosis.

The IRP came to be accepted as the optimal manometric marker of impaired deglutitive EGJ relaxation and EGJ outflow obstruction based on landmark studies that determined normal values in a cohort of healthy controls. A cutoff normal value in healthy subjects of <15 mmHg for 5mL water swallows was based on a comparison with well-defined, unequivocal achalasia patients, where it was found to differentiate between the two with a very high degree of accuracy.[20,21] While this undoubtedly remains the case, IRP seems to lack sensitivity in more subtle cases. This seems to be a particular problem when there is minimal esophageal pressurization; in this setting a sufficient esophago-gastric pressure gradient cannot develop so IRP is sometimes not raised, despite clear evidence of bolus holdup.[22] In such a scenario, it may only be after larger volumes of liquid or solids fill the esophagus that the obstruction becomes apparent and is measurable.[6,11,12]. Indeed, there were more cases of Type I achalasia with dilated esophagus in the normal IRP group than in standard achalasia controls. The Chicago Classification attempts to take some of these limitations into account, stating that in the presence of absent contractility, achalasia should be considered when IRP values are borderline and when there is evidence of esophageal pressurization.[5] Yet we described normal IRP achalasia in all three achalasia subtypes, IRP values were not just borderline but often very low (a quarter of patients had IRP less than 4), and further, pan-esophageal pressurization was not seen in most of these subjects on the standard 5mL water swallows on which the Classification is based.

When performing testing with RDC and solid swallows, the presence or absence of pan-esophageal pressurization was used as the marker of impaired deglutitive EGJ relaxation as this is invariably consequent to outflow obstruction, and therefore highly suggestive of achalasia.[22] This is a reliable and easily determined metric that can be applied between centers and is independent of hardware-specific values, and in turn, adds to the generalizability of the findings. Indeed, we found no difference in outcomes in normal IRP patients between the two study sites or based upon the HRM system used. Device-specific normal values for RDC and solid swallows exist, and it is possible that by using those, the sensitivity of such adjunctive tests for achalasia could be increased even further. In this study, solid swallows were less often helpful in diagnosing LES obstruction compared to RDC and TBE. While our protocol consisted of administration of sequential single solid swallows, a standardized meal has been shown to significantly improve sensitivity to identifying LES obstruction.[6,12]

Limitations of the present study relate to its retrospective nature and include the fact that the HRM protocol for additional provocative testing differed in some ways between the study sites. However, this enabled the inclusion of various techniques and technologies, all of which aimed to demonstrate that resistance to flow across the EGJ is impaired. This study did not aim to identify which additional provocative test is superior, rather, that further testing should be undertaken over and above standard HRM with 5mL water swallows in accordance with local expertise and technologies. Further, the choice of achalasia therapy was not standardized and left to the discretion of the treating physician. However, this

reflects therapeutic decision-making in real world scenarios, and in any case the type of primary therapy administered was highly concordant between groups.

In summary, a protocol including combinations of rapid drink challenge, solid swallows and barium esophagogram, performed adjunctively to standard HRM with 5mL water swallows, identifies EGJ outflow obstruction in a group of achalasia-like patients who are not identified by standard testing. Furthermore, patients identified in this way demonstrated a favorable response to achalasia therapy, suggesting that they do indeed have achalasia with clinically relevant EGJ obstruction. The findings reinforce that despite being considered the gold standard diagnostic test, standard HRM can miss the diagnosis of important motility disorders. Therefore in the appropriate clinical setting some form of additional provocative testing, such as the types that we describe, should be performed over and above the standard HRM protocol, to ensure the optimum sensitivity for diagnosis of achalasia such that appropriate therapy can be administered. Future, larger studies should prospectively examine outcomes in normal IRP achalasia following standardized treatment protocols.

Acknowledgements

The authors wish to thank Ms. Zhixin Liu of the University of New South Wales, Australia, for advice regarding statistical analysis.

Grant support/ Disclosures/ Writing support: Nil to declare from any authors

Abbreviations

EGJ, esophago-gastric junction; FLIP, functional lumen imaging probe; HRM, high-resolution manometry; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; POEM, per-oral endoscopic myotomy; RDC, rapid drink challenge, TBE, timed barium esophagogram

Author contributions

Study concept and design: SSanagapalli, SR, RS; data acquisition: SSanagapalli, SR, AH, KP, AR, MB, RS; analysis and interpretation of data: SSanagapalli, RS; drafting of manuscript: SSanagapalli; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: SSanagapalli; administrative, technical and other material support: MB, RH, LL, DG, SSami

References

1. Boeckxstaens GE, Annese V, des Varannes S, et al. Pneumatic Dilation versus Laparoscopic Heller's Myotomy for Idiopathic Achalasia. *The New England Journal of Medicine.* 2011;364(19):1807-1816.
2. Inoue H, Sato H, Ikeda H, et al. Per-oral endoscopic myotomy: a series of 500 patients. *Journal of the American College of Surgeons.* 2015;221(2):256-264.
3. El-Takli I, O'Brien P, Paterson WG. Clinical diagnosis of achalasia: how reliable is the barium x-ray? *Canadian Journal of Gastroenterology and Hepatology.* 2006;20(5):335-337.

4. Howard PJ, Maher L, Pryde A, Cameron EW, Heading RC. Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. *Gut.* 1992;33(8):1011-1015.

5. Kahrilas PJ, Bredenoord AJ, Fox M, et al. The Chicago Classification of esophageal motility disorders, v3.0. *Neurogastroenterology & Motility.* 2015;27(2):160-174.

6. Sweis R, Anggiansah A, Wong T, Brady G, Fox M. Assessment of esophageal dysfunction and symptoms during and after a standardized test meal: development and clinical validation of a new methodology utilizing high‐resolution manometry. *Neurogastroenterology & Motility.* 2014;26(2):215-228.

7. Daum C, Sweis R, Kaufman E, et al. Failure to respond to physiologic challenge characterizes esophageal motility in erosive gastro-esophageal reflux disease. *Neurogastroenterology & Motility.* 2011;23(6):517.

8. Wang YT, Tai LF, Yazaki E, et al. Investigation of Dysphagia After Antireflux Surgery by High-resolution Manometry: Impact of Multiple Water Swallows and a Solid Test Meal on Diagnosis, Management, and Clinical Outcome. *Clinical gastroenterology and hepatology.* 2015;13(9):1575-1583.

9. Sanagapalli S, Emmanuel A, Leong R, et al. Impaired motility in Barrett's esophagus: A study using high‐resolution manometry with physiologic challenge. *Neurogastroenterology & Motility.* 2018;30(8):e13330.

10. Sweis R, Heinrich H, Fox M. Variation in esophageal physiology testing in clinical practice: Results from an international survey. *Neurogastroenterology & Motility.* 2018;30(3):e13215.

11. Ang D, Hollenstein M, Misselwitz B, et al. Rapid Drink Challenge in high‐resolution manometry: an adjunctive test for detection of esophageal motility disorders. *Neurogastroenterology & Motility.* 2016;29(1):e12902.

12. Ang D, Misselwitz B, Hollenstein M, et al. Diagnostic yield of high-resolution manometry with a solid test meal for clinically relevant, symptomatic oesophageal motility disorders: serial diagnostic study. *The Lancet Gastroenterology & hepatology.* 2017;2(9):654-661.

13. Ponds FA, Bredenoord AJ, Kessing BF, Smout A. Esophagogastric junction distensibility identifies achalasia subgroup with manometrically normal esophagogastric junction relaxation. *Neurogastroenterology & Motility.* 2016;29(1):e12908.

14. Lin Z, Carlson DA, Dykstra K, et al. High‐resolution impedance manometry measurement of bolus flow time in achalasia and its correlation with dysphagia. *Neurogastroenterology & Motility.* 2015;27(9):1232-1238.

15. Salvador R, Savarino E, Pesenti E, et al. The Impact of Heller Myotomy on Integrated Relaxation Pressure in Esophageal Achalasia. *Journal of Gastrointestinal Surgery.* January 01 2016;20(1):125-131.

16. Kessing BF, Weijenborg PW, Smout AJPM, Hillenius S, Bredenoord AJ. Water-perfused esophageal high-resolution manometry: normal values and validation. *American Journal of Physiology-Gastrointestinal and Liver Physiology.* 2014;306(6):G491-G495.

17. de Oliveira JM, Birgisson S, Doinoff C, et al. Timed barium swallow: a simple technique for evaluating esophageal emptying in patients with achalasia. *American journal of roentgenology.* 1997;169(2):473-479.

18. Annese V, Basciani M, Perri F, et al. Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. *Gastroenterology.* 1996;111(6):1418-1424.

19. Vaezi MF, Baker ME, Achkar E, Richter JE. Timed barium oesophagram: better predictor of long term success after pneumatic dilation in achalasia than symptom assessment. *Gut.* 2002;50(6):765-770.

20. Ghosh SK, Pandolfino JE, Rice J, Clarke JO, Kwiatek M, Kahrilas PJ. Impaired deglutitive EGJ relaxation in clinical esophageal manometry: a quantitative analysis of 400 patients and 75 controls. *American Journal of Physiology - Gastrointestinal and Liver Physiology.* 2007;293(4):G878-G885.

21. Pandolfino JE, Ghosh SK, Zhang Q, Jarosz A, Shah N, Kahrilas PJ. Quantifying EGJ morphology and relaxation with high-resolution manometry: a study of 75 asymptomatic volunteers. *American Journal of Physiology-Gastrointestinal and Liver Physiology.* 2006;290(5):G1033-G1040.

22. Lin Z, Kahrilas PJ, Roman S, Boris L, Carlson D, Pandolfino JE. Refining the criterion for an abnormal Integrated Relaxation Pressure in esophageal pressure topography based on the pattern of esophageal contractility using a classification and regression tree model. *Neurogastroenterology & Motility.* 2012;24(8):e356-e363.

23. Sanagapalli S, Sweis R. Achalasia: It Is Not All Black and White. *Current Gastroenterology Reports.* 2017;19(6):27.

Table 1: Baseline clinical characteristics

	Normal IRP achalasia	Controls	P
N	29	29	
Median age, years	50 (39-60)	56 (42-68)	0.14
Male, n (%)	14 (48%)	11 (38%)	0.43
Treatment naïve, n (%)	16 (55%)	20 (69%)	0.28
Achalasia subtype, n			
I	16	6	0.02
II	11	20	
III	2	3	
Median IRP of ten 5mL water swallows, mmHg	8 (4-12)	29 (20-35)	<0.0001
Barium stasis at 5 min on TBE at baseline, cm	12 ± 7 (*N*=17)	15 ± 8 (*N*=20)	0.14
Eckardt score at baseline	6 (5-7)	7 (6-9)	0.01

Data expressed as median (interquartile range), mean ± SD, or total (percentage)

Table 2: Evidence for non-relaxing LES in Normal IRP achalasia subjects

Panesophageal pressurization with RDC, n (%)	22/28 (79%)
Panesophageal pressurization with solid swallows, n (%)	7/14 (50%)
Stasis on barium esophagogram, n (%)	23/29 (79%)

Figure 1: Discrimination of study groups by test findings. Between 2013 and 2017, 4975 subjects underwent esophageal HRM across both sites for all indications. 357 subjects had raised IRP and were diagnosed with achalasia, of which 29 consecutive patients comprised the standard achalasia control group. 29 subjects comprised the normal IRP achalasia group with findings indicating LES obstruction on additional provocative tests (rapid drink challenge, solid swallows and/or barium esophagogram), and after the exclusion of insufficiently symptomatic patients.

Figure 2: Venn diagram describing the combinations of positive investigations used to diagnose achalasia in those with normal integrated relaxation pressure during 5mL water swallows

Figure 3: Additional provocative tests to diagnose achalasia despite normal IRP in a 40-year-old female with longstanding dysphagia to both liquids and solids. (A): representative HRM topographic plot of a 5mL water swallow, demonstrating aperistalsis but normal IRP (11mmHg), therefore not ordinarily diagnostic for achalasia. (B) and (C): representative topographic plots during RDC and solid swallows respectively, both demonstrating pan-esophageal pressurization. (D): marked holdup of contrast on barium esophagogram. (B) to (D) were all indicative of inadequate LES relaxation, therefore patient was treated with pneumatic dilatation, resulting in excellent symptomatic and radiological improvement. Adapted with permission from "Achalasia: it is not all black and white," by S. Sanagapalli and R. Sweis, 2017, *Current Gastroenterology Reports*, 19, p. 27. Copyright 2017 by Springer Science+Business Media New York.[23]

Figure 4: Choice of primary therapy in normal IRP achalasia cases and standard achalasia controls. PD, pneumatic dilation; POEM, per-oral endoscopic myotomy.

Figure 5: Similar short-term (3 month) symptom response to therapy in normal IRP achalasia cases and standard achalasia controls. Horizontal black line indicates Eckardt score of 3, below which defines adequate symptom control.