Physiological augmentation of esophageal distension pressure and peristalsis during conditions of increased esophageal emptying resistance.

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Abstract

Background: Abdominal compression has been implemented as a provocative maneuver in high-resolution impedance manometry (HRIM) to 'challenge' normal esophageal physiology, with the aim of revealing abnormal motor patterns which may explain symptoms. In this study we measured the effects of abdominal compression on esophageal functioning utilizing novel pressure-impedance parameters and attempted to identify differences between healthy controls and globus patients. **Methods:** Twenty-two healthy volunteers (aged 23-32 years, 41% female) and twenty-two globus patients (aged 23-72 years, 68% female) were evaluated with HRIM using a 3.2 mm water perfused manometric and impedance catheter. All participants received 10x5mL liquid swallows; healthy controls also received 10x5mL liquid swallows with abdominal compression created using an inflatable cuff. All swallows were analyzed to assess esophageal pressure topography (EPT) and pressure-flow metrics, indicative of distension pressure, flow timing and bolus clearance were derived. **Key Results:** The effect of abdominal compression was shown as a greater contractile vigor of the distal esophagus by EPT, and higher distension pressure based on pressure-flow metrics. Age and body mass index also increased contractile vigor and distension pressure. Globus patients were similar to controls. **Conclusions & Interferences:** Intrabolus pressure and contractile vigor are indicative of the physiological modulation of bolus transport mechanisms. Provocative testing by abdominal compression induces changes in these esophageal bolus dynamics.

Keywords: abdominal compression, esophageal high-resolution manometry, globus, impedance, pressure-flow analysis

Key Points:

- Abdominal compression has been implemented as a provocative maneuver in high-resolution impedance manometry to ‘challenge’ normal esophageal physiology. In this study we measured the effects of abdominal compression on esophageal functioning utilizing novel pressure-impedance parameters.

- The effect of abdominal compression was shown as a greater contractile vigor of the distal esophagus, and higher distension pressure based on pressure-flow metrics.

- Both application of novel pressure-impedance parameters and abdominal compression may help to reveal underlying esophageal dysfunction.

Introduction

State-of-the art high-resolution manometry (HRM) has improved knowledge of esophageal function through an enhancement of spatial resolution due to increasing pressure sensor numbers. This evolution continued with the establishment of esophageal pressure topography (EPT) metrics[1,2] and wide spread translation into clinical practice through the definition of the Chicago Classification (CC) algorithm for diagnosis of esophageal motor disorders (current version 3.0).[3] The CC utilizes, among other things, the integrated relaxation pressure (IRP4s) to define the extent of relaxation of the lower esophageal sphincter (LES). Failure of relaxation, defining achalasia and its subtypes, is the starting point for the algorithm, followed by esophagogastric junction (EGJ) outflow obstruction, distal esophageal spasm, and ineffective motility (IEM).

A now recognized limitation of the CC lies in the lack of an association of standard esophageal pressure topography metrics with dysphagia symptoms.[4] This limitation has led to the evolution of adjunctive measurements utilizing esophageal impedance topography in combination with manometry to directly link pressure measurements to aberrant bolus transport.[5,6] In addition, provocative testing protocols have been implemented in order to 'challenge' normal esophageal physiology, with the aim of revealing abnormal motor patterns which may explain symptoms. One way of challenging the esophagus is using solid boluses,[7-10] another is to apply abdominal compression extrinsically via a gastric cuff. By artificially increasing the gastric pressure, the cuff creates an outflow resistance against which the esophageal propulsion must work.[11-13]

Esophageal dysmotility has been observed in globus patients.[14] However, studies using HRM with impedance for obtaining more comprehensive information are limited.[15]

In the current study we examined the effect of the application of a gastric cuff on novel pressure-impedance parameters of esophageal function during bolus swallowing. Our secondary aim was to determine whether novel pressure-impedance analysis can identify subtle differences in the physiological swallowing response that may exist between globus patients and healthy participants. We hypothesized that, in healthy participants, extrinsic abdominal compression would cause increased distension pressures in the esophageal body during bolus transport and that novel pressure-impedance analysis could detect the anticipated physiological changes in distension and contractile pressures.

Methods

The study protocol was approved by the Research Ethics Committee of the Hualien Tzu Chi Hospital, Taiwan.

Subjects

Twenty-two healthy volunteers (aged 23-32 years, mean age 26 years, 13M) recruited by a community advertisement were included in this study. None of them had a prior history of upper gastrointestinal complaints or any history of esophageal, gastric or duodenal disease. Twenty two globus patients (aged 23-72 years, mean age 52 years, 7M) that were having non-painful sensation of a lump or foreign body in the throat without dysphagia or odynophagia for more than 3 months were also included. Exclusion criteria included prior history of esophageal motility disorder, nasolaryngeal tumor or surgery. Patients did not have evidence of mechanical obstruction on barium esophagogram or esophagoscopy performed less than three months before the study. Any medication that could affect upper gastrointestinal motility was discontinued in the week prior to study. All participants gave written informed consent prior to the study.

High-resolution impedance manometry equipment

High resolution impedance manometry (HRIM) was performed using a 10 French (3.2 mm diameter) water perfused manometric and impedance catheter (Mui Scientific, Mississauga, Canada) with 36 x 1 cm spaced side-hole sensors 12 x 2 cm impedance segments (straddling pressure sensors P8-32). The luminal diameter of each perfusion capillary was 0.4 mm and the total diameter was 4.7 mm. Data were recorded with external pressure transducers (Argon Medical Devices, Plano, Texas, United States of America). Pressure and impedance data were

acquired at 20 Hz (Solar GI acquisition system; Medical Measurement Systems, Enschede, The Netherlands).

Study protocol

After overnight fasting, the impedance/manometry assembly was passed into the esophagus through a lignocaine spray anesthetized nostril. The catheter was zeroed to atmospheric pressure before it was introduced. The catheter was placed with at least three distal sensors positioned in the stomach, in order to record from hypopharynx till proximal stomach. While in the supine position, each healthy control subject was given ten liquid swallows of 5 mL (0.9% saline) at 30-s intervals, followed by ten 5 mL swallows with abdominal compression. During swallowing, the abdominal compression was performed with a flexible belt around upper abdomen and subcostal areas, which was applied tightly with a blood pressure cuff (Omron, Taiwan) under the belt. This was inflated to a constant cuff pressure of 60 mmHg. The cuff was deflated between swallows.[16,17] During abdominal compression, the interval between the swallows was set at least 30 seconds immediately after deflating the cuff. Globus patients underwent a procedure involving capture of liquid swallows, however abdominal compression was not performed in these patients.

Data analysis

Esophageal pressure topography

All recorded swallows were analyzed and the averages of the liquid swallows during each experimental condition were compared.

Standard EPT variables were measured using the semi-automated *Quickview for HRM* software, these were: 4-s integrated relaxation pressure (IRP4s; mmHg), distal contractile

integral (DCI; mmHg.cm.s), contractile front velocity (CFV; cm/s), distal latency (DL; s), and largest break (cm).[3]

Pressure-Flow Analysis

Automated analysis (FIGURE 1) was applied to each swallow using purpose built software (*Esophageal AIMplot*, copyright T. Omari) programmed in MatLab (The MathWorks Inc., Natick, Massachusetts, United States of America). Data based on *AIMplot* software algorithms have been previously published.[18-22] However for this work, the software underwent substantial revision focusing on variables that have demonstrated relevance in past studies. The derivation of these variables is described in detail below:

Following uploading of swallow data in comma separated values (.csv) format, the user selected key temporal and anatomical landmarks from a pressure topography plot (swallow onset, esophageal proximal margin, transition zone, crural diaphragm and stomach). A separate pressure topography plot was generated upon which superimposed lines showed the position of the Nadir Impedance (indicating peak distension) and Contractile Peak over time (FIGURE 1 A). The user then fine adjusted landmarks paying particular attention to the contractile deceleration point (CDP) time and position, the crural diaphragm position and the angle of the contractile font. Three classes of pressure-flow variable were then algorithmically derived as described below:

Bolus Flow Latencies (FIGURE 1 B) were determined based on the pressure and impedance recording at the level of the CDP. *Swallow to Distension Latency* (SDL) was defined as the time from swallow (UES relaxation onset) to the Nadir Impedance Point (NI) indicative of peak distension. *Distension to Contraction Latency* (DCL) was defined as the time from NI to

the Contractive Front (CF) indicative of lumen occlusive contraction. The sum of these sub-latencies equates to the Distal Latency (DL, standard esophageal pressure topography metric).

Intra-Bolus Distension Pressures during bolus transport (FIGURE 1 C) was determined by the pressure measured at Nadir Impedance indicative of the pressure when the lumen is at its maximal cross-sectional area. Three separate distension pressures were determined along the esophagus. These were based upon anatomical regions and were designed to reflect distension pressure during different phases of bolus transport. These were the mean *Distension Pressure during the Accommodation Phase* (DPA, based on pressures from UES to TZ), *Compartmentalized Transport Phase* (DPCT, based on pressures from TZ to CDP) and the *Esophageal Emptying Phase* (DPE, based on pressures from CDP to CD).[23]

Intra-Bolus Ramp Pressure is indicative of bolus pressurization during luminal contraction within the distal esophagus (FIGURE 1 D). This was measured over time from Nadir Impedance to Contractile Front at and immediately above the CDP region (sensors within distal 25% of the TZ to CDP length; see points 0 (at CDP), +1 and +2 cm in panel A). The *Ramp Pressure* (RP) is determined by the mean gradient of pressure change over time.

Effectiveness *Bolus Clearance* mechanisms was determined from TZ to CDP based on the relationship of the Nadir Impedance to the Impedance at the Contractile Peak (FIGURE 1 E). A higher *Impedance Ratio* (IR) equates to *less* effective bolus clearance.[22]

In addition to the above, we included the measurement trans-EGJ *Bolus Flow* based on the method of Lin.[24] The measurement of Bolus Flow Time (BFT) was based on three impedance and three manometry signals were positioned through the EGJ at 1-cm intervals with the distal impedance and pressure signals positioned aligned with crural diaphragm contractions. Using the impedance signals, the duration of bolus presence (called *Bolus Presence Time,*

BPT) was determined (onset of bolus presence defined by impedance drop to 90% of the nadir; offset defined as the return to 50% of the impedance baseline). Using the manometry signals the flow-permissive pressure gradient periods (i.e. esophageal pressure > crural and gastric pressure) within to the overall period of bolus presence were identified. BFT was defined by the sum of the flow permissive pressure gradient periods. A shorter BFT is indicative of reduced esophageal emptying.[24]

Statistical analysis

Statistical tests were performed using IBM SPSS 22 (SPSS Inc, Chicago, United States of America). Subject average data for each experimental condition were derived. Paired data were compared using Student's paired t-test or Wilcoxon sign rank test if data failed Shapiro-Wilk normality testing. ANOVA (General Linear Model) was used for group comparisons and to explore interactions with other potential influencers such as IEM diagnosis, age and BMI. Kruskal Wallis test was used for group comparisons when data failed Shapiro-Wilk normality testing. Correlation was tested using Spearman's rho correlation. Data are expressed as estimated marginal means ± standard error if normally distributed or otherwise median [interquartile range]. Significance was accepted at a p-value < 0.05; however p-values of 0.05-0.099 are also shown.

Results

All study participants successfully completed the HRIM measurement and no adverse events occurred. One healthy participant was excluded from analysis as the swallow protocol was incomplete due to intolerance of the catheter. Two globus patients were also excluded from analysis due to technical problems with the recording quality. Compared to controls, globus patients were younger (average 25 ± 3 vs. 50 ± 11 years, t 9.634, p<.001) but were of similar body weight and BMI (average weight 69 ± 13 vs. 69 ± 15 kg respectively, t = -.004, ns; BMI 24 ± 4 vs. 26 ± 4 kg m^{-2} respectively, t = 1.470, ns).

Chicago Classification (V3.0)

Of 21 evaluable studies of healthy control subjects, three met criteria for IEM and the remainder showed normal motility. Of 19 evaluable globus patients, one patient fulfilled CC criteria for *absent contractility* and this patient was therefore excluded on grounds of having a major motor disorder. Six globus patients met criteria for IEM and the others were all normal (number of IEM diagnoses in patients *vs* controls not statistically significant; Fisher Exact Test, p = 0.265). Apart from weak esophageal contractility, overall, an IEM diagnosis was associated with *lower* distal intrabolus pressures (DPCT t 2.233, p.032; DPE t 2.488, p .017; RP t 3.118, p .003), *shorter* bolus flow time across the EGJ (t 2.162, p .037) and a *higher* impedance ratio signifying greater bolus residual (t -2.060, p .057).

Effect of Abdominal Compression

The effects of the abdominal compression protocol on controls are shown in TABLE 1. Utilizing standard EPT metrics, abdominal compression resulted in greater contractile vigor of the distal esophagus, indicated by a higher DCI, reduced peristaltic break size and decreased IRP4s.

Utilizing Pressure-Flow metrics (TABLE 1), abdominal compression resulted in higher distension pressures (DPCT and DPE). Esophageal nadir impedance, corresponding to maximum luminal cross-sectional area, decreased consistent with greater dilation of esophageal lumen under the greater distension pressure. The contractile peak impedance was unchanged by abdominal compression suggesting that bolus clearance was unaffected, this, combined with the lower nadir impedance, caused a net decrease in impedance ratio. Bolus flow latencies and bolus flow time were not affected by abdominal compression.

Effect of Age, Weight and Body Mass Index

Amongst all participants, we observed significant correlations between older age, greater weight and/or BMI for some variables (TABLE 2). Most notably, significant associations with *higher* distal intrabolus pressures, *shorter* BFT (age only), *slower* CFV (vs. age and BMI only) and *greater* distal contractility (vs. weight only); together suggesting that older and heavier participants showed evidence of greater flow resistance during esophageal emptying.

Controls vs. Patients with Globus Sensation

In comparing the study measures calculated for controls and patients with globus sensation, the presence of an IEM diagnosis and participant age and BMI were included in the general linear model in order to account for their previously described effects. The analysis of main effects in relation to globus sensation revealed no significant differences, however trends suggestive of *longer* DL, *slower* CFV and *longer* BPT in patients were observed (TABLE 3). The previously characterized associations of older age and higher BMI with distal intrabolus pressures were also significant within the model (DPE only, TABLE 3).

Relationship between Intrabolus Pressure and Esophageal Body Contractility

Based on previous observations that a higher distal intrabolus distension pressure has a physiological tendency to correlate with greater distal contractile vigour,[18,20] we investigated this relationship again within the current dataset, examining the contractile response in both the proximal and distal esophageal segments. Intrabolus pressures measured proximally (DPA) did not correlate with contractility, nor did distal intrabolus pressures correlate with proximal contractility. However, the participants with higher distal intrabolus pressure values (DPE and RP) demonstrated greater contractility of the distal esophageal body (higher DCI). When this relationship was examined in the control and globus groups separately, the significant correlation only persisted for controls (TABLE 4).

Discussion

In this study we utilized esophageal high-resolution impedance manometry and a range esophageal pressure topography and pressure-flow variables to examine the physiological response of the esophagus to abdominal compression, a provocative maneuver designed to increase esophageal emptying resistance through an increase in intra-gastric pressure. Further we compared asymptomatic healthy individuals to a group of patients experiencing globus sensation. The main findings were as follows; i. bolus swallows performed when abdominal compression was applied showed an increase in the distension pressure and augmented contractile vigor of the esophageal body, the latter being most likely a physiological response to increased esophageal emptying resistance, ii. factors such as age and BMI may also augment distension pressure and the vigor of the esophageal contractility most likely by increasing emptying resistance, iii. when these factors were taken into account, patients with globus sensation do not demonstrate overt differences in esophageal function compared to controls, and iv. the normal pattern of increasing esophageal contractility in relation to greater distension pressure, whilst present in controls was largely absent in globus patients.

The current study further explored the potential additive value of esophageal impedance measurement used in combination with manometry. Pressure-flow analysis directly integrates the separate impedance and pressure recordings in order to objectively derive a number of novel parameters indicative of flow timing, luminal area, bolus presence, 'distension' and 'ramp' intrabolus pressures and bolus clearance. It has been proposed that these parameters may reveal important aspects of normal esophageal physiology, and, by directly linking pressure to bolus flow/transport, and the relative interplay of distension pressures to the contractile response, can potentially reveal abnormal motor patterns which may explain symptom generation.[6,22,25]

The abdominal compression protocol is designed to increase esophageal outflow resistance by artificially increasing the gastric pressure. Past studies in animal models and human subjects[26-28] have shown that gastric compression leads to outflow resistance as evidenced by an increase in esophageal intrabolus pressure during bolus transport. This is in turn associated with an increase in the contractile pressure generated by the esophagus. This 'reactive augmentation' of peristalsis, represents the normal physiological response to changes in outflow resistance and is most likely due to the fact that resistance proportionately alters the pre-, and after-load tension properties of the muscle during the contractile phase.[20] Furthermore, changes in pressure and diameter will in turn modify circumferential tension within the esophageal wall stimulating sensory afferents that can modulate intrinsic neuro-mechanical responses which, in the distal esophagus, are under enteric nervous system control.[25]

The current study confirms these effects. Specifically, when abdominal compression was applied, we showed an increase in the distension pressure and a lower nadir impedance (shown to correlate with increased luminal cross-sectional area).[29] These changes are biomechanically consistent with augmented passive distension of the distal esophagus. The passive distension was in turn associated with augmented vigor of contraction of the esophageal body that follows. Similar changes were also seen in relation to participant age and BMI, suggesting that these factors also increase esophageal emptying resistance. Based on previous studies, older age has shown to reduce esophageal compliance and neurogenic relaxation of the lower esophageal sphincter,[30] while higher BMI results in higher gastric pressure due increased abdominal fat .[31]

Even though very highly sensitive methodologies were used, the globus patients were not significantly different to controls when confounders such as age and BMI were taken into

account. This reaffirms that overt dysmotility is not a common feature of globus sensation patients.[32] Previous studies, have reported inconsistent differences in patients with globus such as motility disorders[33,34] and IEM (also seen here but not significant) as well as incomplete bolus transit.[14]

When more subtle features of esophageal sensory-motor function were explored some differences were apparent. The positive correlation of distension and contractile pressures seen in the current study has been reported in previous studies[18,20] and others have also described this relationship existing in reflux patients following fundoplication surgery.[35,36] It is well established that, in a non-obstructed EGJ setting, esophageal contractility does not determine intrabolus pressures. This is because most pressure generation occurs after luminal closure and is located above the intrabolus pressure domain where the distension pressures are measured.[37,38] Hence it is the presence of the bolus that augments contractility, as was demonstrated by Dodds et al (1973)[39] who showed that bolus distension during swallowing produces higher peak pressures and longer slower contractions (findings which translate in the modern era to an increase in the DCI metric). Data from the current study suggest that this known relationship between bolus distension and the contractile response may be perturbed in globus patients, thus the mechanisms underlying reactive augmentation may be aberrant. Whilst the abdominal compression protocol may further help elucidate these differences, the method in our hands has only to date been applied to controls.

In conclusion, the characterization of intrabolus pressure, contractile vigor and the inter-relationships between, are indicative of the physiological modulation of bolus transport mechanisms. Provocative testing by abdominal compression induces changes in these esophageal bolus dynamics.

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Disclosures

T.I. Omari hold inventorship of Australian patent 2011301768 that covers some of the analytical methods described.

Author contributions

Study concept and design: Chen, Omari. *Acquisition, analysis, or interpretation of data:* Chen, Brink, Lei, Omari, Singendonk. *Drafting of the manuscript:* Chen, Brink, Omari, Singendonk, Lei, Hung, Liu, Yi. *Critical revision of the manuscript for important intellectual content:* All authors. *Administrative, technical, or material support:* Chen. *Study supervision:* Chen, Omari.

Abbreviations

AC = abdominal compression

AIM = automated impedance manometry

ANOVA = analysis of variance

BFT = bolus flow time

BPT = bolus presence time

CC = Chicago Classification version 3.0

CD = crural diaphragm

CDP = contractile deceleration point

CF = contractive front

CFV = contractile front velocity

DCI = distal contractile integral

DCL = distension to contraction latency

DL = distal latency

DPA = distension pressure during the Accommodation Phase

DPCT = distension pressure during the Compartmentalized Transport Phase

DPE = distension pressure during the Esophageal Emptying Phase

EGJ = esophagogastric junction

EPT = esophageal pressure topography

GERD = gastroesophageal reflux disease

HRM = high resolution manometry

HRIM = high resolution impedance manometry

IEM = ineffective motility

IR = impedance ratio

IRP = integrated relaxation pressure

IRP4s = 4-s integrated relaxation pressure

LES = lower esophageal sphincter

NI = nadir impedance point

PCI = proximal contractile integral

RP = ramp pressure

SDL = swallow to distension latency

SEM = standard error of the mean

TZ = transition zone

UES = upper esophageal sphincter

References

1 Kahrilas, P. J. & Pandolfino, J. E. High resolution manometry. *UpToDate* (December 2016).
2 Kahrilas, P. J. Esophageal motor disorders in terms of high-resolution esophageal pressure topography: what has changed? *The American journal of gastroenterology* 105, 981-987 (2010).
3 Kahrilas, P. J. *et al.* The Chicago Classification of esophageal motility disorders, v3. 0. *Neurogastroenterology & Motility* 27, 160-174 (2015).
4 Xiao, Y. *et al.* Lack of correlation between HRM metrics and symptoms during the manometric protocol. *The American journal of gastroenterology* 109, 521-526 (2014).
5 Omari, T., Tack, J. & Rommel, N. Impedance as an adjunct to manometric testing to investigate symptoms of dysphagia: What it has failed to do and what it may tell us in the future. *United European gastroenterology journal*, 2050640614549096 (2014).
6 Carlson, D. *et al.* High-resolution impedance manometry parameters enhance the esophageal motility evaluation in non-obstructive dysphagia patients without a major Chicago Classification motility disorder. *Neurogastroenterology & Motility* 29 (2017).
7 Dooley, C. P., Di Lorenzo, C. & Valenzuela, J. E. Esophageal function in humans. *Digestive diseases and sciences* 35, 167-172 (1990).
8 Keren, S., Argaman, E. & Golan, M. Solid swallowing versus water swallowing: manometric study of dysphagia. *Digestive diseases and sciences* 37, 603-608 (1992).
9 Johnston, B. T., Collins, J. S., McFarland, J., Blackwell, J. N. & Love, A. A comparison of esophageal motility in response to bread swallows and water swallows. *American Journal of Gastroenterology* 88 (1993).
10 Bernhard, A., Pohl, D., Fried, M., Castell, D. O. & Tutuian, R. Influence of bolus consistency and position on esophageal high-resolution manometry findings. *Digestive diseases and sciences* 53, 1198-1205 (2008).
11 Goldani, H. A., Fernandes, M. I. M., Vicente, Y. A. & Dantas, R. O. Lower esophageal sphincter reacts against intraabdominal pressure in children with symptoms of gastroesophageal reflux. *Digestive diseases and sciences* 47, 2544-2548 (2002).
12 Dodds, W. J. *et al.* Effect of increased intraabdominal pressure on lower esophageal sphincter pressure. *The American journal of digestive diseases* 20, 298-308 (1975).
13 Mittal, R. *et al.* Human lower esophageal sphincter pressure response to increased intra-abdominal pressure. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 258, G624-G630 (1990).
14 Chen, C.-L., Yi, C.-H. & Liu, T.-T. Association between swallow perception and esophageal bolus clearance in patients with globus sensation. *Digestive diseases and sciences* 58, 1042-1048 (2013).
15 Yanova, O., Lazebnik, L., Kim, V., Firsova, L. & Bordin, D. Esophageal disorders and psychological disadaptation in patients with globus sensation. *Neurogastroenterology & Motility* 24, 163 (2012).
16 Kahrilas, P., Lin, S., Chen, J. & Manka, M. The effect of hiatus hernia on gastro-oesophageal junction pressure. *Gut* 44, 476-482 (1999).
17 Janssen, P., Verschueren, S. & Tack, J. Intragastric pressure as a determinant of food intake. *Neurogastroenterology & Motility* 24, 612-e268 (2012).
18 Omari, T., Kritas, S. & Cock, C. New insights into pharyngo-esophageal bolus transport revealed by pressure-impedance measurement. *Neurogastroenterology & Motility* 24, e549-e556 (2012).

19 Rohof, W. O. *et al.* Inter- and intra-rater reproducibility of automated and integrated pressure-flow analysis of esophageal pressure-impedance recordings. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 26, 168-175, doi:10.1111/nmo.12246 (2014).
20 Omari, T. I., Wauters, L., Rommel, N., Kritas, S. & Myers, J. C. Oesophageal pressure-flow metrics in relation to bolus volume, bolus consistency, and bolus perception. *United European gastroenterology journal* 1, 249-258 (2013).
21 Rommel, N., Van Oudenhove, L., Tack, J. & Omari, T. I. Automated impedance manometry analysis as a method to assess esophageal function. *Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society* 26, 636-645, doi:10.1111/nmo.12308 (2014).
22 Omari, T. *et al.* Correlation of esophageal pressure-flow analysis findings with bolus transit patterns on videofluoroscopy. *Diseases of the Esophagus* 29, 166-173 (2016).
23 Lin, Z. *et al.* The four phases of esophageal bolus transit defined by high-resolution impedance manometry and fluoroscopy. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 307, G437-G444 (2014).
24 Lin, Z. *et al.* Flow time through esophagogastric junction derived during high-resolution impedance-manometry studies: a novel parameter for assessing esophageal bolus transit. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 307, G158-G163 (2014).
25 Leibbrandt, R. E. *et al.* Characterization of esophageal physiology using mechanical state analysis. *Frontiers in systems neuroscience* 10 (2016).
26 Boyle, J. T., Altschuler, S. M., Nixon, T. E., Pack, A. I. & Cohen, S. Responses of feline gastroesophageal junction to changes in abdominal pressure. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 253, G315-G322 (1987).
27 Mittal, R., Ren, J., McCallum, R., Shaffer, H. & Sluss, J. Modulation of feline esophageal contractions by bolus volume and outflow obstruction. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 258, G208-G215 (1990).
28 Ren, J. *et al.* Effect of increased intra-abdominal pressure on peristalsis in feline esophagus. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 261, G417-G425 (1991).
29 Kim, J. H., Mittal, R. K., Patel, N., Ledgerwood, M. & Bhargava, V. Esophageal distension during bolus transport: can it be detected by intraluminal impedance recordings? *Neurogastroenterology & Motility* 26, 1122-1130 (2014).
30 Cock, C. *et al.* Age-related impairment of esophagogastric junction relaxation and bolus flow time. *World journal of gastroenterology* 23, 2785 (2017).
31 El-Serag, H. B., Tran, T., Richardson, P. & Ergun, G. Anthropometric correlates of intragastric pressure. *Scandinavian journal of gastroenterology* 41, 887-891 (2006).
32 Chen, C., Szczesniak, M. & Cook, I. Evidence for oesophageal visceral hypersensitivity and aberrant symptom referral in patients with globus. *Neurogastroenterology & Motility* 21, 1142 (2009).
33 Färkkilä, M. A. *et al.* Globus pharyngis, commonly associated with esophageal motility disorders. *American Journal of Gastroenterology* 89 (1994).
34 Wilson, J. *et al.* Estimation of oestrogen and progesterone receptors in chronic rhinitis. *Clinical Otolaryngology & Allied Sciences* 11, 213-218 (1986).
35 Scheffer, R., Samsom, M., Frakking, T., Smout, A. & Gooszen, H. Long-term effect of fundoplication on motility of the oesophagus and oesophagogastric junction. *British journal of surgery* 91, 1466-1472 (2004).

36 Myers, J. *et al.* Susceptibility to dysphagia after fundoplication revealed by novel automated impedance manometry analysis. *Neurogastroenterology & Motility* 24, 812-e393 (2012).
37 Brasseur, J. G. & Dodds, W. J. Interpretation of intraluminal manometric measurements in terms of swallowing mechanics. *Dysphagia* 6, 100-119 (1991).
38 Ren, J. *et al.* Determinants of intrabolus pressure during esophageal peristaltic bolus transport. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 264, G407-G413 (1993).
39 Dodds, W., Hogan, W., Reid, D., Stewart, E. & Arndorfer, R. A comparison between primary esophageal peristalsis following wet and dry swallows. *Journal of applied physiology* 35, 851-857 (1973).

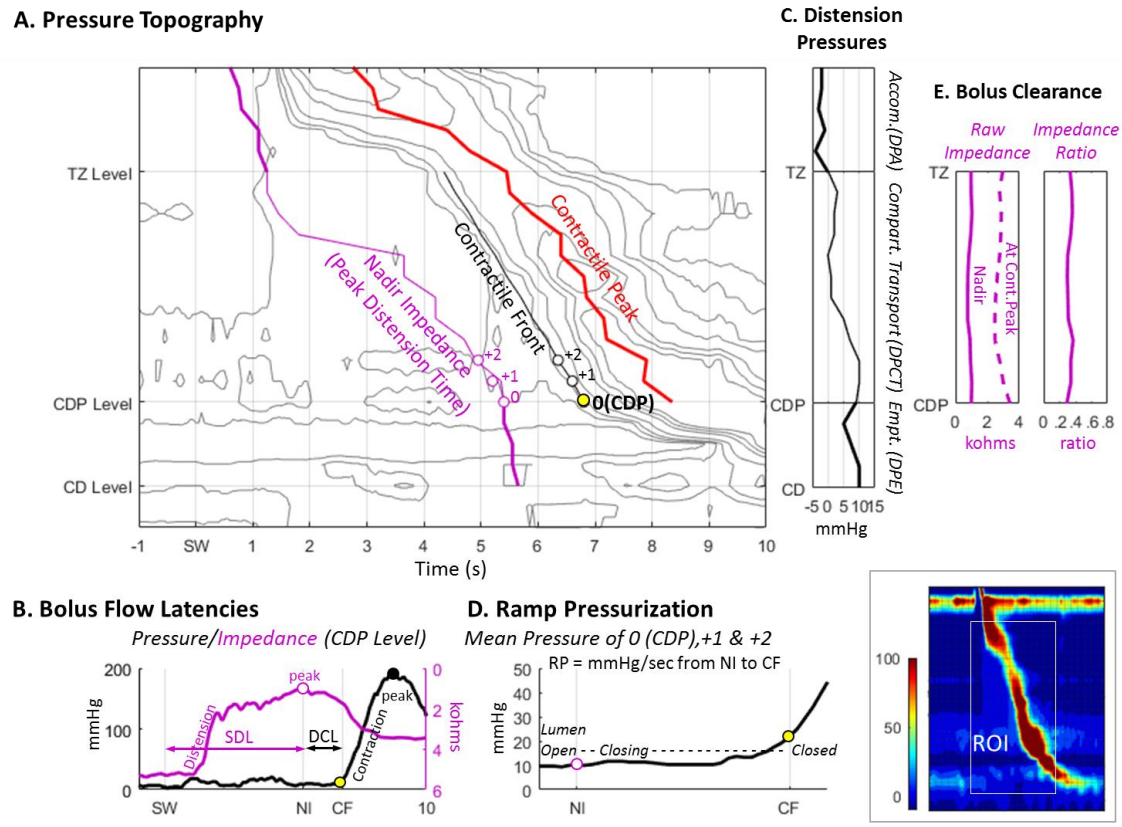

FIGURE 1. **Derivation of Pressure-Flow metrics.** Automated analysis was applied to each swallow within a region of interested (see inset lower right). **A.** A pressure topography iso-contour plot with superimposed lines showing the position of the Nadir Impedance (thick purple line; indicating peak distension) and Contractile Peak (thick red line) over time. The analyst fine adjusted landmarks paying particular attention to the Transition Zone (TZ), the Contractile Deceleration Point (CDP; yellow dot), Crural Diaphragm (CD). **B.** *Bolus Flow Latencies* were determined based on the pressure and impedance recording at the CDP level. These were the Swallow to Distension Latency (SDL) from swallow to Nadir Impedance (NI) and Distension to Contraction Latency (DCL) from NI to Contractile Front (CF). **C.** *Intra-Bolus Distension Pressure* during bolus transport was determined as the Pressure at Nadir Impedance which was determined along the esophagus based on the average Distension Pressure (DP) within three anatomical regions approximating the different phases of bolus transport. These were DP during bolus accommodation (DPA, pressures UES to TZ), DP during compartmentalized transport (DPCT, pressures TZ to CDP) and the DP during esophageal emptying (DPE, pressures from CDP to CD). **D.** *Intra-Bolus Ramp Pressurization* was measured over time from NI to CF within the distal esophagus (25% of TZ to CDP length; see points 0 (at CDP), +1 and +2 cm in Panel A). The Ramp Pressurization (RP) was determined by the mean gradient of pressure change over time. **E.** Effectiveness *Bolus Clearance* was determined from TZ to CDP based on the Impedance Ratio (IR = NI/Impedance at Contractile Peak). A higher IR equates to *less* effective bolus clearance.

Variable	Before AC	During AC	Effect of AC (t, p-value)
EPT			
PCI (mmHg.s.cm)	208 ± 26	233 ± 28	ns
DCI (mmHg.s.cm)	936 ± 99	1275 ± 155	-2.943, .008
DL(s)	7.5 ± 0.2	7.4 ± 0.2	ns
CFV (cm/s)	4.9 [4.0, 5.6]	4.4 [3.8, 5.7]	ns
Largest Break (cm)	1.9 [1.2, 2.8]	1.3 [0.3, 2.5]	2.330, .02
IRP4s (mmHg)	5.0 [4.0, 6.5]	3.0 [0.5, 4.0]	3.463, .001
Pressure Flow Analysis			
Bolus Flow Latencies			
SDL(s)	4.0 ± 0.3	3.9 ± 0.3	ns
DCL(s)	2.5 [1.8, 3.3]	2.3 [1.8, 3.3]	ns
Intra-Bolus Pressure			
DPA(mmHg)	4.9 ± 0.9	5.7 ± 1.0	ns
DPCT(mmHg)	5.2 ± 0.7	6.1 ± 0.7	-2.599, .017
DPE(mmHg)	5.4 ± 0.6	6.1 ± 0.6	-2.111, .048
RP (mmHg/s)	12.9 ± 1.4	14.6 ± 1.8	ns
Bolus Clearance			
Nadir Imp.(kohms)	1.20 [1.09, 1.27]	1.01 [0.94, 1.12]	2.833, .005
Imp.Cont.Peak(kohms)	2.58 ± 0.13	2.55 ± 0.13	ns
Impedance Ratio	0.50 ± 0.02	0.44 ± 0.02	4.473, <.001
Trans-EGJ Bolus Flow			
BPT (s)	4.1 ± 0.3	4.3 ± 0.3	ns
BFT(s)	1.7 ± 0.3	1.9 ± 0.2	ns

TABLE 1. Effect of abdominal compression (AC) on variables generated during liquid swallows in healthy subjects. Data are means ± SEM or median [IQR]. Paired t-test parameters or Wilcoxon sign rank test (t statistic, p-value) are shown when the p-value was <0.1.

Variable	Age	Weight	BMI
EPT			
PCI	-.132	.252	.150
DCI	-.054	**.353***	.255
DL	.015	-.017	-.033
CFV	**-.331***	-.239	**-.366***
Largest Break	.043	-.230	-.134
IRP4s	.143	-.113	.060
Pressure Flow Analysis			
Bolus Flow Latencies			
SDL	.248	.238	.243
DCL	.035	-.299	-.221
Intra-Bolus Pressure			
DPA	-.012	.189	.133
DPCT	-.019	.171	.140
DPE	**.353***	.291	**.464****
RP	-.092	**.361***	**.342***
Bolus Clearance			
Nadir Imp.	.129	-.087	.038
Imp.Cont.Peak	.033	-.014	.121
Impedance Ratio	.158	-.050	-.079
Trans-EGJ Bolus Flow			
BPT	-.211	.070	.103
BFT	**-.383***	-.083	-.115

TABLE 2. Spearman's rho correlation between variables and overall participant characteristics. Correlation is significant (2-tailed; *p<0.05, **p<0.01).

Variable	Control Group	Globus Group	Effect of Group (F, p-value or t, p)	Effect of IEM Pattern (F, p-value or t, p)	Effects of Age & BMI
EPT					
PCI (mmHg.s.cm)	162 ± 57	245 ± 53	ns	ns	ns
DCI (mmHg.s.cm)	734 ± 148	634 ± 138	ns	↓26.57, <.001	ns
DL(s)	6.9 ± 0.5	8.3 ± 0.5	↑3.335, .077	ns	ns
CFV (cm/s)	4.9 [4.0, 5.6]	4.1 [3.3, 4.4]	↓7.585, .006	ns	-
Largest Break (cm)	1.7[1.2, 2.8]	2.2 [0.3, 4.6]	ns	↑3.712, <.001	-
IRP4s (mmHg)	5.0 [4.0, 6.5]	6.0 [4.0, 9.0]	ns	ns	-
Pressure Flow Analysis					
Bolus Flow Latencies					
SDL(s)	3.6 ± 0.4	4.1 ± 0.4	ns	↑3.538, .069	ns
DCL(s)	2.5 [1.8, 3.3]	2.3 [1.9, 3.2]	ns	↑2.138, .031	-
Intra-Bolus Pressure					
DPA(mmHg)	-1.6 ± 11.4	5.8 ± 10.6	ns	ns	ns
DPCT(mmHg)	5.2 ± 1.4	3.2 ± 1.3	ns	↓4.132, .050	ns
DPE(mmHg)	6.0 ± 1.1	5.5 ± 1.1	ns	↓8.722, .006	↑Age*,↑BMI**
RP (mmHg/s)	12.0 ± 2.5	8.4 ± 2.3	ns	↓6.613, .015	ns
Bolus Clearance					
Nadir Imp.(kohms)	1.20 [1.09, 1.27]	1.21 [1.16, 1.33]	ns	ns	-
Imp.Cont.Peak(kohms)	2.4 ± 0.2	2.5 ± 0.2	ns	↓4.510, .041	ns
Impedance Ratio	0.53 ± 0.04	0.52 ± 0.03	ns	ns	ns
Trans-EGJ Bolus Flow					
BPT (s)	2.6 ± 0.5	4.2 ± 0.5	3.260, .080	↓6.553, .015	↓Age*
BFT(s)	0.9 ± 0.4	1.8 ± 0.4	ns	↓4.499, .041	ns

TABLE 3. Comparison of Healthy Subjects and Globus Patients.

Data are either estimated marginal means ± SEM based on ANOVA (General Linear Model with Group and IEM Pattern as between subject fixed factors and Age and BMI as a covariates) or medians [IQR] based on Kruskal Wallis test (Group comparisons only). The ANOVA parameters (F statistic, p-value) or Kruskal Wallis test parameters (standardized t statistic, p-value) are only shown when the p-value was <0.1. Other effects in relation to age and BMI are indicated for variables where General Linear Model was appropriate (*indicates level of significance; *p<0.05, **p<0.01). Arrows (↑↓) indicate the directionality of the influence of an IEM pattern, age or BMI.

		Contractile Pressure					
		PCI			**DCI**		
	Group	All	Control	Globus	All	Control	Globus
Intrabolus Pressure	**DPA**	-.042	-.140	.004	.304	.230	.339
	DPE	-.087	.221	-.258	**.454****	**.457***	.425
	RP	.027	.117	-.158	**.450****	**.584****	.300

TABLE 4. Correlation of measures of distension pressure and esophageal body contractility. Spearman's rho correlation between variables overall and separate groups. Correlation is significant (2-tailed; *p<0.05, **p<0.01).