

Inter- and Intra-Rater Reproducibility of Automated and Integrated Pressure-Flow Analysis of Esophageal Pressure-Impedance Recordings

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ABBREVIATIONS: AIMplot, automated impedance manometry analysis; EGJ, esophago-gastric junction; GERD, gastro-esophageal reflux disease; HRM, high-resolution manometry;

HRIM, high-resolution impedance manometry; ICC, intraclass correlation coefficient; IRP4, 4-s integrated relaxation pressure; LES, lower esophageal sphincter.

SHORT RUNNING HEADER: Reproducibility of Esophageal AIMplot

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Abstract

INTRODUCTION: Automated impedance manometry pressure-flow analysis (AIM analysis) determines pressure measurements relative to bolus flow and has to date shown subtle variations in esophageal motility in relation to dysphagia. In this study we assessed intra- and inter-rater reproducibility of AIM- metrics derived using purpose designed software.

METHODS: Fifty patients referred for evaluation of gastro-esophageal reflux symptoms (33 men, age 52 ± 1.9 years) underwent combined high resolution impedance manometry and completed a dysphagia questionnaire. From 10 liquid and 10 viscous swallows, a subset of 4 swallows (2 saline and 2 viscous) were systematically selected from each patient for manual and *AIMplot* analysis, which was performed twice by 5 observers (2 experts, 3 non-experts). Intra- and inter-rater agreement were determined using intraclass correlation coefficients.

RESULTS: *AIMplot* based analysis showed high intra-rater and inter-rater reproducibility for all metrics (mean ICCs of 0.95 and 0.94 respectively). Reproducibility of metrics derived for liquid and viscous did not differ (ICCs of 0.96 and 0.91 for liquid and viscous respectively). In addition, metrics derived by experts had an equivalent level of reproducibility compared to non experts (ICCs of 0.96 and 0.94 respectively). Variables that could be derived with commercial software (ManoView™) correlated highly with variables from *AIMplot* based analysis, such as 4-s integrated relaxation pressure ($r=0.85$) and the 20 mmHg isobaric contour defect ($r=0.92$).

CONCLUSION: Esophageal *AIM* analysis is highly reproducible, independent of an observer's level of experience in esophageal motility. Therefore *AIM* analysis produces data that is reliable for clinical and research purposes.

KEY WORDS: Esophagus, Esophageal manometry, Electrical impedance, Reproducibility, Dysphagia.

Introduction

The Chicago classification establishes normative values and guidelines for evaluation of high-resolution manometry (HRM) based on analysis of pressure measurements to determine the integrity of esophageal peristalsis and relaxation of the esophagogastric junction.^{1, 2} Although well-described esophageal motility disorders such as achalasia and distal esophageal spasm are detected with high accuracy by applying this classification, more subtle abnormalities are often classified as ineffective or even ‘normal’ motility.³ High-resolution impedance manometry (HRIM) displays better the dynamics of esophageal bolus flow and the pressures driving it, with the potential to allow for exploration of more subtle differences in esophageal motility that may be associated with normal and abnormal bolus flow and the perception of symptoms.^{3, 4}

Recently, we developed a novel automated impedance manometry analysis method (*AIM analysis*). AIM analysis was first developed to assess pharyngeal swallowing where it can determine pharyngeal dysfunction predisposing to ineffective swallowing and aspiration risk.⁸ In this setting, the method demonstrated excellent reproducibility in experienced and inexperienced hands.⁹ In pilot studies in the esophagus based on conventional low resolution pressure-impedance recording, AIM analysis appears to detect esophageal dysfunction predisposing to post-fundoplication dysphagia in GERD patients.^{5, 6} Most recently, AIM analysis metrics have been shown to differentiate non-obstructive dysphagia patients with normal manometry from controls, underlining the potential of AIM analysis to shed new light on currently incompletely understood clinical issues.⁷

AIM analysis is relatively simple to perform with the aid of software (called *AIMplot*) which generates objective metrics describing flow and pressure in the esophagus and at the level of the esophagogastric junction (EGJ).^{8, 9} However, to be applicable for clinical or research purposes, a high level of reproducibility is required. Hence the aim of this study was

to determine the intra- and inter-rater variability of *AIM* analysis. In addition, our secondary aim was to explore the association of *AIMplot* variables with the reporting of dysphagia.

Methods

Patients

We analysed pressure-impedance data from HRIM performed in 50 adult patients referred for evaluation of persistent gastroesophageal reflux disease (GERD) symptoms (33 men, mean age 52 ± 1.9 years, range 25-73 years). The study protocol was approved by the ethics committee of the Royal Adelaide Hospital and all patients gave written informed consent prior to enrolment into the study.

Measurement protocol

Patients were studied lying in the left-lateral position after a 6 hour fast. A solid-state HRIM catheter (Sierra Scientific Instruments, Los Angeles, CA, USA) with 36 pressure sensors spaced 1 cm apart and 18 2-cm adjoining impedance segments was utilised. After insertion through an anaesthetized nostril, the catheter was placed so that it straddled both esophageal sphincters, with at least 3 cm located in the stomach. Pressure and impedance data were acquired at 50 Hz using ManoScan™ (Sierra Scientific Instruments, Los Angeles, CA, USA). The protocol included 10 by 5-mL saline swallows (0.1N NaCl) and 10 by 5-mL viscous swallows (Viscous swallow challenge media, Sandhill Scientific, Highland Ranch, CO, USA) after a 5 minute adjustment period.

In addition, patients completed a symptom assessment questionnaire, including a validated dysphagia questionnaire assessing dysphagia for 9 different food types with increasing viscosity (water to meat; scale 0-45; no dysphagia 0).¹⁰

High-resolution impedance manometry and AIM analysis

A test database was compiled which contained 200 de-identified swallows; four for each patient comprising the first and sixth liquid and viscous swallow. Failed swallows were

excluded from the analysis, as is not possible to apply AIM to a swallow without any contractility. If first or sixth swallow corresponded to a completely failed swallow, we included the subsequent swallow. Manometry and impedance data were initially analysed using ManoView software (Sierra Scientific Instruments, Los Angeles, CA, USA) to determine the following variables: (1) 4-s integrated relaxation pressure (IRP4); (2) hiatal hernia size; (3) axial length of the break in peristalsis using the 20 mmHg isobaric contour line and (4) presence of retrograde bolus escape/ incomplete bolus clearance as described previously.³

For AIM analysis, raw impedance and manometry data of each swallow were exported in ASCII text format and analysed using *AIMplot*, a purpose-designed MATLAB based (MathWorks, Natick, MA, USA) program. Data were interpolated to increase the amount of spatial and temporal data points as previously described.^{9, 11, 12} Subsequently, each observer performed AIM analysis by defining the following four landmarks in the spatiotemporal plot (Figure 1.): (1) The onset of the swallow, defined by the onset of upper esophageal sphincter relaxation, (2) the onset of the esophageal pressure wave, (3) the position of the transition zone and (4) the upper margin of the esophagogastric junction. Guided by these landmarks, *AIMplot* then automatically derived 56 variables of which eight are listed in Table 1.

Observers

Five observers with varied experience in esophageal manometry participated in the study. Two observers, considered experts, routinely performed and analysed esophageal motility, whilst 3 other observers (1 medical doctor, 1 medical student and 1 speech pathologist) had little or no experience in esophageal motility measurements. After a 5-minute introduction to the *AIMplot* program, observers undertook a practice run by analysing 5 swallows. After the

introduction, each observer analysed the data set twice in their own time over a two week period.

Data and statistical analysis

Statistical analysis was performed using SPSS 16.0 (IBM corporation, Somers, NY, USA). Data are presented as mean \pm SEM when parametric, and as median (interquartile range, IQR) when non-parametric. Intra-class correlation coefficients (ICC) were determined as the mean ICC of each rater in case of intra-rater agreement, which is also known as the test/retest reproducibility. For inter-rater variability, the multiple measurements ICC were determined using the variables from the first analysis run from each observer. The scale of correlations was evaluated as follows: 0.00-0.20, slight agreement; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial and 0.81-1.00 excellent. Bivariate correlations were determined for manual and *AIMplot* data using Pearson's correlation coefficient, and evaluated using the same correlation scale. A Student's t-test was used to compare mean values for parametric data. All p-values were derived from two-sided statistical analyses and regarded as statistically significant when $p < 0.05$.

Results

Chicago Classification

Based on a primary diagnostic analysis of pressure topography (performed by Author JCM) 0 patients (0%) had esophageal motility disorders such as diffuse spasm, nutcracker or aperistalsis. Using standard Chicago Classification definitions (2), 28 patients (56%) had normal peristalsis, 11 (22%) of patients had weak peristalsis (6 patients with large breaks), 10 patients (20%) had frequent failed peristalsis; 1 patient (2%) had hypertensive peristalsis and 0 patients (0%) had EGJ obstruction.

Observer variability

AIMplot based analysis was completed twice for all 200 swallows by all observers. *AIM* analysis variables had high intra-rater reproducibility (mean ICC of 0.95, Table 2.) and inter-rater reproducibility (mean ICC of 0.94). Reproducibility for *AIMplot* analysis of liquid and viscous swallow variables were both high, although mean ICC values for liquid swallows were slightly higher than viscous swallows (ICCs of 0.96 and 0.91 respectively, Table 2.). Subsequently we compared two observers with substantial experience with esophageal motility measurements to three observers with limited or no experience. Variables from *AIM* analysis by experts had excellent ICC (0.96), which was comparable to the ICC of non-experts (0.94). *AIM* yields variables for proximal and distal esophageal motility, with the transition zone defining the border between the two regions. The mean ICC for the distal esophagus was higher compared to the proximal esophagus (0.97 vs 0.87), though both ICCs are considered excellent.

Agreement with Esophageal Pressure Topography variables

To further validate *AIMplot* based analysis, a comparison was made between the computer assisted analysis of data using ManoView™ software (Sierra Scientific Instruments of Given

Imaging, Los Angeles, CA, USA), with the mean values for data derived automatically from *AIMplot* analysis undertaken by the five observers. For the axial length of the break in peristalsis using the 20 mmHg isocontour line there was a high concordance of findings ($r=0.92$ $p<0.001$) and a similar finding was found for IRP4 ($r=0.85$, $p<0.001$) as measured by *ManoView* and *AIMplot*.

Incomplete bolus transfer, dysphagia and AIM analysis

To assess the clinical value of variables derived with *AIMplot*, we explored the relation of these variables with dysphagia. Of 50 patients, 20 patients (40%) reported mild or moderate dysphagia, with a mean Dakkak and Bennett score 17 ± 0.9 (range 4-35) out of 45. An evaluation of EGJ metrics found IRP4 did not significantly differ for swallows in patients with dysphagia compared to those without dysphagia (4.9 ± 0.5 mmHg vs. 4.9 ± 0.6 mmHg, $p<0.94$). In addition, there was no difference in the manometric size of hiatal hernia or nadir EGJ pressure in patients with or without dysphagia (1.0 ± 0.3 cm vs. 0.7 ± 0.3 cm, $p=0.47$ and 0.7 ± 0.3 mmHg vs. 0.7 ± 0.5 mmHg for no dysphagia compared to dysphagia respectively).

Subsequently we analysed the relation of incomplete bolus clearance and dysphagia. Incomplete bolus clearance was determined manually for each swallow using *ManoView* software (Figure 2). For all 200 swallows, 134 demonstrated complete bolus clearance from the esophagus, while clearance was incomplete for 66 swallows. Incomplete bolus clearance was observed in significantly more swallows from patients with dysphagia compared to patients without dysphagia (43% vs. 26%, $p<0.05$, Chi-square).

Lastly we utilised data from *AIMplot* analysis to evaluate swallows with incomplete bolus clearance with regard to the axial length of the break in peristalsis or isocontour defect (Figure 2.). A significantly longer 20 mmHg isobaric contour defect was observed for swallows with incomplete bolus clearance compared to swallows with complete bolus transfer (7.0 ± 0.5 cm

vs. 1.6 ± 0.2 cm, $p < 0.0001$ Student's t-test, Figure 3.). Further, mean intrabolus pressure was significantly lower in swallows with incomplete bolus transfer compared to those with complete bolus transfer (7.0 ± 0.6 mmHg vs. 9.6 ± 0.6 mmHg, $p < 0.001$).

AIMplot calculates a unique variable, namely the mean impedance at the time of the peak pressure of peristalsis. A low impedance level represents bolus presence and we found swallows with incomplete clearance had a significantly lower impedance value at peak pressure than those swallows with complete bolus clearance ($506 \pm 27 \Omega$ vs. $861 \pm 43 \Omega$, $p < 0.001$), indicating bolus presence at the level of esophageal contraction with the highest amplitude. This is also illustrated by the ratio of nadir impedance and the impedance at peak pressure. During swallows with complete bolus clearance, the ratio of nadir impedance to the impedance at peak pressure is significantly smaller compared to incomplete clearance (0.31 vs 0.41, $p < 0.001$). In line with this, the impedance at peak peristaltic pressure showed a significant correlation with the length of the 20 mmHg isobaric contour defect ($r = -0.43$, $p < 0.0001$). This indicates that a large isocontour defect is associated with a greater volume of retrograde bolus flow.

Discussion

We hypothesized that *AIM* analysis will be a useful tool in the analysis of esophageal motility and bolus transport. To be a reliable tool for clinical or research purposes *AIMplot* needs to be reproducible in the hands of novices and experts alike. In the current study we demonstrated that *AIM* analysis by *AIMplot* software has a highly reproducible output by all users, showing that observers were able to reproducibly select the four spatio-temporal landmarks defining the regions of interest required for automated analysis algorithms to produce outputs. In addition, we validated *AIM* analysis by comparing *AIMplot* derived variables to computer assisted and manually determined variables with proven clinical value such as IRP4 and the axial length of the 20 mmHg isobaric contour defect. We conclude that *AIMplot* based analysis is an objective and reliable method that can now be used to better understand esophageal motility and bolus transport.

Since the introduction of HRIM, our knowledge of esophageal motility has improved markedly. Due to the increase in the number of pressure sensors, features of esophageal motor function such as the transition zone and contraction deceleration point have been characterised and are better understood. Previously, Fox *et al* demonstrated using concurrent HRM and videofluoroscopy that the increased spatial resolution of HRM was able to show segmental hypotensive foci, which were associated with incomplete bolus transit. Subsequently, the addition of impedance to esophageal manometry has added an easy and reliable assessment of bolus transport, as validated with videofluoroscopy by the excellent correlation of nadir impedance values and bolus transport in a study by Imam *et al* ¹³. Automated analysis of impedance and pressure data, i.e. *AIMplot* analysis generates objective and quantifiable variables. In the current study, we demonstrated that intra- and inter-rater agreement of *AIM* analysis were excellent for both esophageal and EGJ variables (ICCs>0.9). This is in line with inter- and intra-rater agreement observed for pharyngeal *AIM* analysis. ⁹

Moreover, in the current study we demonstrated a high correlation with manually and computer assisted variables and the *AIMplot* derived variables, comparable to the agreement found in pharyngeal *AIMplot* and fluoroscopy. Taken together, these results demonstrate that esophageal *AIMplot* is a reliable and highly reproducible tool for esophageal motility analysis.

A potential weakness of this study is that the studies analysed were performed in patients with GERD, rather than patients referred for symptoms of dysphagia who may demonstrate other esophageal motor disorders, such as hypertensive peristalsis, diffuse esophageal spasm, rapid contraction front velocity and/or short distal latency. Whilst these disordered patterns were not represented in our cohort, we have previously applied AIM analysis to broad dysphagia populations.⁽⁸⁾ GERD patients were evaluated due to the availability of a large database and the fact that dysphagia is relatively common in this population, with a prevalence of 16 – 42% reported in the literature.^{14, 15} In our study, 40% of patients experienced mild to moderate dysphagia in addition to symptoms of heartburn and regurgitation. Despite the high prevalence, the cause of dysphagia in these patients is not understood. In these GERD patients with dysphagia, there were no manometric signs of EGJ obstruction or impairment of relaxation, such as a high nadir EGJ pressure, high IRP4 or high intrabolus pressure. In fact, distal intrabolus pressure was significantly lower in patients with dysphagia, hence rather than increased intrabolus pressure in patients with a functional obstruction or impairment of esophageal outflow, these patients lacked the ability to pressurise the bolus in the esophagus due to poor peristaltic integrity. This finding is in line with the findings of a previous study by Myers *et al*, which demonstrated that LES pressure and intrabolus pressure are low in patients with GERD yet patients with a hiatus hernia had greater incidence of dysphagia.¹⁴ In addition, Pandolfino *et al* demonstrated that GERD patients with hiatus hernia have a lower EGJ pressure, and a higher EGJ distensibility

compared to controls.¹⁶ This suggests that dysphagia in most of these patients is not related to an outflow obstruction at the level of the EGJ.

The association between hypotensive abnormalities of esophageal function and gastroesophageal reflux disease (GERD) is well established. Hypotensive abnormalities are observed in 21- 38% of GERD patients,¹⁷ and are associated with increased acid exposure and reflux symptoms.¹⁷ However, whether dysphagia is in part attributable to ineffective esophageal motility and impaired bolus transport in the esophageal body is controversial. Lazarescu *et al* failed to find a correlation between weak peristalsis, bolus flow and the perception of dysphagia, both in volunteers and GERD patients using combined conventional manometry/impedance.¹⁸ In contrast, in a recent study by Bogte *et al* it was demonstrated that patients with dysphagia had stasis defined as residue in the esophagus after peristalsis in 61% of swallows, compared to 41% of swallows in healthy volunteers. In patients with dysphagia, more peristaltic abnormalities such as weak or absent peristalsis were observed. By adding impedance to HRM, Roman *et al* demonstrated that in swallows with normal EGJ relaxation and morphology, peristaltic contractions with breaks >2 cm in the 20 mmHg isobaric contour are associated with incomplete bolus clearance. Furthermore, longer breaks were associated with more bolus escape.³ Using *AIMplot* analysis we confirmed that longer breaks in peristalsis correlate with retrograde bolus flow. Importantly, we demonstrated that in the absence of a high IRP4, a considerable 20 mmHg isobaric contour defect is required before retrograde flow occurs. Moreover, we objectified the conditions associated with retrograde bolus flow by means of measuring the impedance values at peak peristaltic pressure. In the case of retrograde bolus escape, impedance values were significantly lower compared to swallows without retrograde escape. Importantly, by using this variable from *AIMplot* analysis, we found that impaired bolus transport was significantly different in patients with dysphagia compared to patients without dysphagia (43% vs. 26%). We conclude that

retrograde escape occurs in swallows with a large isobaric contour defect, and we propose that this might be a contributing factor to the perception of dysphagia in the studied cohort of GERD patients.

The strength of our study is that we tested reproducibility of *AIMplot* analysis in a large cohort of patients and selected a variety of observers with different backgrounds and varying experience. By doing so, we demonstrated that the use of *AIMplot* requires minimal training, and yields highly reproducible results. A possible limitation of our study is that we selected only 4 swallows per patient for blinded analysis. Since swallow characteristics are variable, this number while adequate for testing reproducibility of data analysis, does limit data interpretation with regard to clinical utility for evaluation of symptoms such as dysphagia. Therefore, although our results are in line with current literature, a more thorough analysis of this and other cohorts is necessary.

In conclusion, this study demonstrates high reproducibility of *AIMplot* data analysis with experienced and inexperienced users. Further studies are required to demonstrate the clinical value of this automated, quantitative and objective esophageal motility analysis tool.

Table 1.

<i>Variable</i>	<i>Description of variable</i>
Peak pressure (mmHg)	Mean peak pressure of the esophageal peristalsis
Pressure at nadir impedance (mmHg)	Mean pressure at the nadir impedance for the bolus
Intrabolus pressure (mmHg)	Mean intrabolus pressure, defined as the median pressure at the midpoint from the time of nadir impedance to peak pressure
20 mmHg isocontour defect (cm)	Axial length of the break in peristaltic wave where the peak pressure does not reach 20 mmHg
Intrabolus pressure slope (mmHg/s)	Change in pressure over time, from pressure at nadir impedance to pressure at midpoint of time from nadir impedance to peak pressure
Time from nadir impedance to peak pressure (s)	Time interval between nadir esophageal impedance and peak esophageal pressure of peristalsis
Impedance at peak pressure (Ω)	Mean impedance at the peak pressure of the esophageal peristalsis
Ratio of nadir impedance and impedance at peak pressure	Ratio of nadir impedance during the liquid bolus compared to mean impedance at the peak pressure of the esophageal peristalsis
Integrated relaxation pressure 4 seconds (IRP4)	Lowest 4-s cumulative relaxation pressure of the esophagogastric junction during a swallow

Table 1. Description of AIMplot analysis pressure-flow variables

Table 2.

<i>Variable</i>	Intra-rater reproducibility (mean ICC [range])	Inter-rater reproducibility (ICC (95%CI))
Peak pressure (mmHg)	0.97 [0.95-0.98]	0.98 (0.97-0.98)
Pressure at nadir impedance (mmHg)	0.97 [0.95-0.99]	0.97 (0.96-0.97)
Intrabolus pressure (mmHg)	0.97 [0.94-0.99]	0.95 (0.94-0.96)
Intrabolus pressure slope (mmHg/s)	0.98 [0.96-0.99]	0.96 (0.96-0.97)
Time from nadir impedance to peak pressure (s)	0.96 [0.88-0.98]	0.95 (0.93-0.96)
Impedance at peak pressure (Ω)	0.96 [0.94-0.98]	0.96 (0.96-0.97)
Size of the 20 mmHg isocontour defect (cm)	0.96 [0.89-0.99]	0.93 (0.91-0.94)
Integrated relaxation pressure 4-s (IRP4)	0.93 [0.92-0.95]	0.90 (0.88-0.92)
<i>Variable</i>	<i>Liquid</i> Inter-rater reproducibility (ICC (95%CI))	<i>Viscous</i> Inter-rater reproducibility (ICC (95%CI))
Peak pressure (mmHg)	0.98 (0.97-0.98)	0.98 (0.97-0.98)
Pressure at nadir impedance (mmHg)	0.98 (0.97-0.98)	0.94 (0.92-0.96)
Intrabolus pressure (mmHg)	0.98 (0.97-0.99)	0.85 (0.81-0.89)
Intrabolus pressure slope (mmHg/s)	0.98 (0.97-0.99)	0.93 (0.91-0.95)
Time from nadir impedance to peak pressure (s)	0.96 (0.94-0.97)	0.86 (0.82-0.90)
Impedance at peak pressure (Ω)	0.97 (0.95-0.98)	0.97 (0.96-0.98)
Size of the 20 mmHg isocontour defect (cm)	0.96 (0.95-0.97)	0.89 (0.86-0.92)
Integrated relaxation pressure 4-s (IRP4)	0.91 (0.88-0.93)	0.89 (0.86-0.92)

Table 2. Intra- and inter-rater reproducibility of variables derived from AIMplot analysis, for all swallows and separately for liquid and viscous swallows. ICC, intraclass correlation coefficient

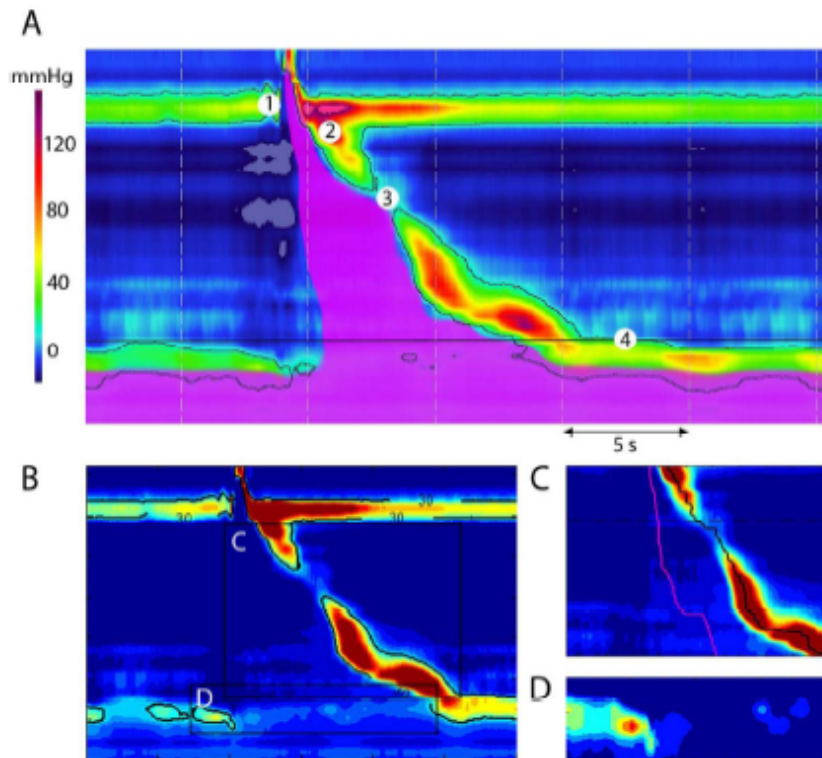
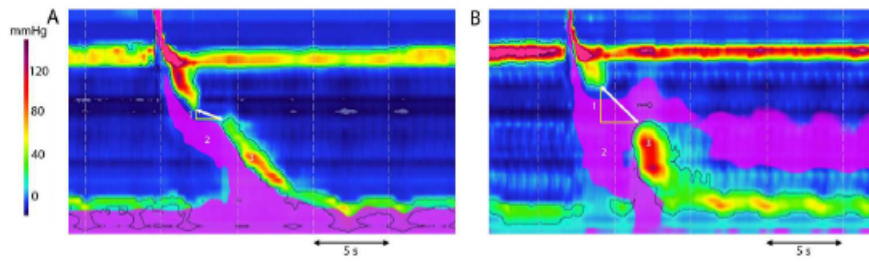


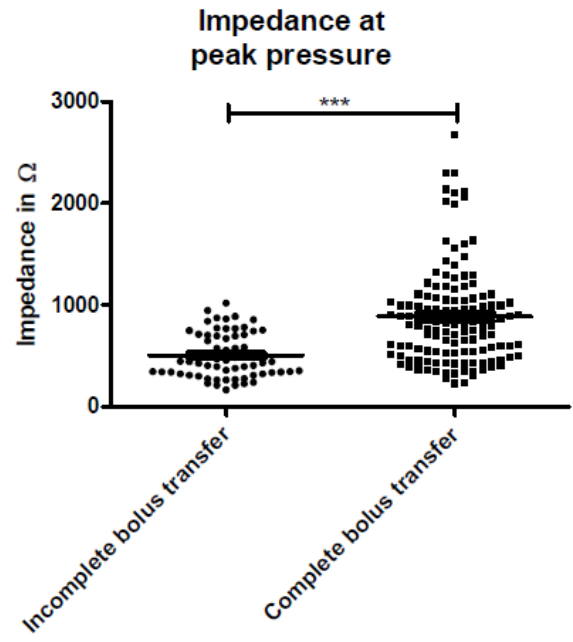
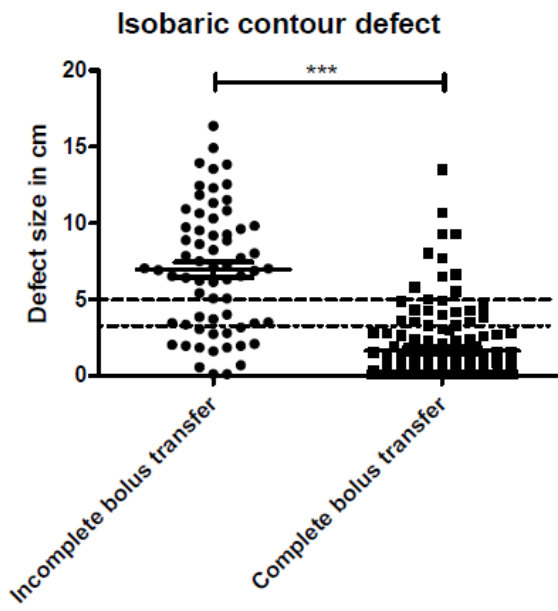
Figure 1 shows a liquid swallow recorded by HRIM, with pressures shown by the coloured spectrum and impedance by the shaded pink (bolus present). The following landmarks depicted in Figure 1A were determined for each swallow by each observer: (1) swallow onset, defined by the onset of upper esophageal sphincter relaxation (2) the onset of the esophageal pressure wave below to the upper esophageal sphincter (3) the position of the transition zone and (4) the upper margin of the esophago-gastric junction. Based on these landmarks AIMplot algorithms created two areas of interest, as shown in Figure 1B. Within the esophageal body (Figure 1C) the peristaltic peak pressure (black line) and the nadir impedance (pink line), are shown.

412x383mm (72 x 72 DPI)



A swallow with complete bolus clearance (2A) and in contrast, a swallow with clear retrograde flow and incomplete bolus clearance (2B). In patients without EGJ obstruction, retrograde flow typically occurred at the level of the 20 mmHg isobaric contour defect, either at the proximal transition zone as in figure 2B, or at the distal transition zone between the contraction deceleration point (CDP) and the EGJ. AIMplot determined the length of the isobaric contour defect (1), the intrabolus pressure (2) and the impedance at peak pressure (3). The length of the 20 mmHg isobaric contour defect was larger when incomplete bolus transport occurred.

746x230mm (72 x 72 DPI)



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