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Esophageal pressure-flow metrics in relation to bolus volume, bolus consistency and bolus perception

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Abbreviations:

AIM	automated impedance manometry
TNadImp	time of nadir impedance
PNadImp	pressure at nadir impedance
IBP	intrabolus pressure
PeakP	peak pressure
TNadImp to PeakP	time of nadir impedance to peak pressure
PFI	pressure flow index
NadImp/ImpPeakP ratio	ratio of nadir impedance to impedance at peak pressure or impedance ratio
FSP	flow stasis point
IRP4s	4 sec integrated relaxation pressure
EGJ	esophago-gastric junction

Abstract

Background: The utility of combined esophageal pressure-impedance recording has been enhanced by automation of data analysis. **Objective:** To understand how esophageal function as measured by automated impedance manometry pressure flow analysis (AIM analysis) varies with bolus characteristics and subjective perception of bolus passage. **Methods:** Esophageal pressure-impedance recordings of 5ml/10ml liquid/viscous swallows and 2cm/4cm solid swallows from 20 healthy control subjects (5male; 25-73 years) were analysed. Metrics indicative of bolus pressurisation (Intrabolus pressure (IBP), IBP slope) were derived. Bolus flow resistance, the relationship between bolus pressurisation and flow timing, was assessed using a pressure flow index (PFI). Bolus retention was assessed using the ratio of Nadir Impedance to Peak Pressure Impedance (impedance ratio). Subjective perception of bolus passage was assessed swallow by swallow. **Results:** Viscosity increased the bolus flow resistance and reduced bolus clearance. Responses to boluses of larger volume and more viscous consistency, revealed a positive correlation between bolus pressurisation and esophageal peak pressure. Flow-resistance was higher in subjects who perceived bolus hold up of solids. **Conclusion:** Bolus volume and bolus type alter esophageal function and impact AIM analysis metrics descriptive of esophageal function. Perception of bolus transit was associated with heightened bolus pressurisation relative to bolus flow.

Introduction

The potential utility of combined esophageal manometry and multichannel intraluminal impedance recording has been recently enhanced by automation of data analysis. In the process of developing automated impedance-manometry pressure-flow analysis (AIM analysis) new metrics were conceived that better describe the interactions between bolus transport and pressure generation. This new approach to integrated analysis is very different from the current application of each analysis type in isolation. AIM analysis was first applied to the assessment of pharyngeal swallowing (1-3), and the first reports of the technique in the esophagus demonstrate potential in relation to elucidating post-fundoplication dysphagia (4, 5) and non-obstructive dysphagia (6). A keystone of this novel approach is the use of impedance to track the trajectory of the bolus centre as it traverses the esophagus (7). The bolus trajectory pathway can therefore provide new insights into the complex interplay between pharyngeal-driven and esophageal-driven bolus transport mechanisms (7). Furthermore, the ability to objectively measure intra-luminal pressure relative to bolus movement and vice-versa, can detect small variations and subtle abnormalities of esophageal function that are not obvious with conventional analysis.

Given the potential clinical utility of this novel method, we undertook a pilot study to understand how esophageal function, as measured by AIM pressure-flow analysis, varies with bolus characteristics and in relation subjective perception of bolus passage. We hypothesised that more viscous bolus consistencies would transit slower and require greater bolus pressurisation and that subjective perception of bolus passage would correlate with alterations in esophageal function as assessed by AIM pressure-flow analysis.

Methods

Subjects and Protocol

The study protocol was approved by the Royal Adelaide Hospital Research Ethics Committee and performed in the University Department of Surgery, Royal Adelaide Hospital. Twenty healthy control subjects (5 males, mean age 48.9 yrs, 25-73 yrs) underwent esophageal high resolution impedance-manometry (HRIM). All subjects were screened for upper gastro-intestinal symptoms, including an assessment of swallowing difficulty to a range of foods using a validated composite dysphagia score (8). All reported no dysphagia symptoms (Scale 0 - 45, 0 = none). Two solid state manometric and impedance catheter configurations were used (10 subjects with each); a 4.0mm diameter catheter incorporating 32 1cm-spaced pressure sensors and 16 adjoining impedance segments, each 2 cm apart (Unisensor USA Inc, Portsmouth, NH, USA), or a 4.0mm diameter catheter incorporating 36 1cm-spaced pressure sensors and 18 adjoining impedance segments, each of 2 cm (Given Imaging Pty Ltd, Los Angeles, CA, USA). Pressure and impedance data were acquired at 50Hz (Insight acquisition system, Sandhill Scientific, Denver, CO, USA or ManoScan acquisition system, Given Imaging Pty Ltd, Los Angeles, CA, USA). Subjects were intubated after application of topical anaesthesia (5% lignocaine spray) to the naso-pharynx. The catheter was positioned with sensors straddling the region from the upper esophageal sphincter (UES) to the stomach.

Subjects were asked to lie supine and the head of the bed was elevated by 30^{o} to achieve a semi-upright posture. After a 10 min accommodation period, subjects were then given 5 x 5ml and 5 x 10ml liquid (0.9% saline); 5 x 5ml and 5 x 10ml viscous (viscosity 450K cPs, supplied by Sandhill Scientific Inc, Highlands Ranch, Denver, CO, USA); as well as 5 x $2cm^2$ and 5 x $4cm^2$ solid. The solid bolus consisted of a square cut from a slice of white bread, onto which normal saline was applied immediately prior to placement into the mouth. Solid swallows were given > 1 min intervals and the subject was asked to chew *ad libitum* and then to swallow it whole. Masticating the bolus incorporates the saline into the bread bolus improving its conductivity while reducing the consistency to that of a highly viscous semisolid.

Subjects were asked to record their perception of the bolus during each swallow using a six-point-scale to define the pattern of transit and intensity of perception (1 = ‘none’, 2=‘raised awareness’, 3=‘slow passage’, 4=‘stepwise passage’, 5=‘obstruction’, 6=‘pain’).

Data analysis

AIM analysis of the pressure-impedance text data files was performed using esophageal *AIMplot,* a purpose designed analysis program written in MATLAB (version 7.9.0.529 R2009b, The MathWorks Inc, Natick, MA, USA). To operate *Esophageal AIMplot* the observer defined five space-time landmarks on a standard pressure iso-contour plot of the esophageal swallow (see Figure 1 A). These were:

I. The time of swallow onset , defined by the onset of upper esophageal sphincter relaxation.
II. The time of peak esophageal pressure at the orad margin of the proximal esophagus (temporal parameter).
III. The position of the proximal margin of the esophageal pressure wave sequence (spatial parameter).
IV. The position of the transition zone, defined as the point of lowest pressure between proximal and distal esophageal pressure wave sequences, or, the distal margin of the proximal oesophageal contraction sequence when the distal esophageal contraction sequence was absent or large (>6cm).
V. The position of the distal margin of the esophageal pressure wave sequence (where peristalsis joins with reconstituted lower esophageal sphincter (LES) post-relaxation pressure).

Guided by these landmarks, *AIMplot* then automatically derived eight esophageal pressure-flow variables, which were calculated for the whole esophagus; proximal esophagus; and distal esophagus. The variables are listed below and shown in Figure 1 B-D:

I. Pressure at nadir impedance (PNadImp, mmHg); the intrabolus pressure recorded when the esophageal lumen is maximally full of bolus.
II. *Peak pressure* (PeakP, mmHg); the pressure recorded at maximum contractile tension.
III. *Median Intrabolus pressure* (IBP, mmHg); the median intrabolus pressure recorded during the phase of transition from a full lumen to an occluded lumen i.e. the median intrabolus pressure recorded during luminal emptying.
IV. *Time interval between nadir impedance and peak esophageal pressure* (TNadImp to PeakP, sec); the time interval of transition from a maximally full lumen to maximal contractile tension.

V. *Intrabolus pressure slope* (IBP slope, mmHg/sec); the rate of change in intrabolus pressure recorded during the phase of transition from a full lumen to an occluded lumen i.e. the rate of pressure change during luminal emptying.

VI. The *pressure flow index* (PFI, also called the dysphagia risk index (4-6)) was developed in the context of post-fundoplication dysphagia and amplifies differences in key AIM analysis metrics seen in relation to the symptom of dysphagia. The PFI was calculated using the formula below, and is higher in circumstances of pressure-flow abnormality: The PFI is calculated using the formula below:

PFI = (IBP * IBP slope)/(TNadImp-PeakP).

VII. The *ratio of nadir impedance to impedance at the time of peak pressure* or the '*impedance ratio'* was calculated as a marker of incomplete bolus transit (9). We hypothesise that the impedance ratio defines the proportion of the bolus present at the time of peak esophageal contraction relative to the bolus present at the time when the bolus is flowing (high ratio = incomplete transit). This is illustrated in Figure 1D and Figure 2 where the calculation of this variable along the length of the esophagus is shown.

VIII. The *flow stasis point* is based on a new analysis which plots the distance a bolus is propelled into the esophagus by a pharyngeal swallow. The flow stasis point analysis has been previously reported (7) and uses the mean curve based on time of nadir impedance during bolus swallows to track the trajectory pathway of the bolus as it moves down the esophagus. Typically the mean time of nadir impedance curve shows the bolus flowing rapidly, followed by deceleration, stasis, and then acceleration again before the bolus approaches the EGJ (Refer to Figure 2B). We hypothesised that the position of stasis (i.e. the position where the flow pattern changes from deceleration to acceleration) represents a *switch* from bolus propulsion due to pharyngeal mechanisms to bolus propulsion due to esophageal mechanisms. The position of the flow stasis point (FSP) was objectively determined from the mean curve using the point of inflexion of a 3rd order polynomial best fit. The position of the flow stasis point was estimated in cm above the EGJ and was also standardised relative to esophageal length which was defined as the distance from UES distal margin to EGJ proximal margin measured during peristalsis.

In addition to the AIM analysis metrics above, we also measured peristaltic break size (i.e. the total axial length of gaps in the 20mmHg isocontour, 10), nadir EGJ pressure during relaxation and the 4 sec integrated relaxation pressure (IRP4s) of the EGJ (10).

Statistics

The individual swallow data determined for each subject were pooled in relation to bolus type and/or volume and then averaged for the purposes of statistical comparisons. Data are expressed as means ± standard error (SE), median ± inter-quartile range (IQR) or least square means ± SE. Repeated measures were compared using t-test or Mann-Whitney Rank Sum Test and One Way Repeated Measures Analysis of Variance (Holm-Sidak method for pairwise differences) or Friedman Repeated Measures Analysis of Variance on Ranks (Tukey Test for pairwise differences). Non-repeated grouped measures were compared using two-way ANOVA allowing for differences related to acquisition system type and the Holm-Sidak method was used for pairwise comparisons. Relationships between continuous variables were assessed using Spearman Rank Order Correlation. Statistical tests were performed using SigmaPlot ver11.0 (Systat Software Inc., Chicago,IL, USA).

Results

Effect of bolus type and volume on measures of esophageal function

Many AIM analysis metrics were notably different in relation to bolus type and these are summarised in Table 1. An increase in bolus viscosity reduced the distance of bolus travel following pharyngeal propulsion, with the flow stasis point being located further above the EGJ. In contrast, bolus volume did not influence the position of flow stasis. Increasing bolus viscosity was associated with an increase in peristaltic peak pressures, IBP and IBP slope, whilst the time interval between when esophagus is maximally full (i.e the level of greatest bolus accumulation) and maximally contracted, TNadImp to PeakP, was shorter. Increasing bolus volume resulted in similar increases in esophageal peak and IBP, however produced the opposite effect on TNadImp to PeakP (longer) and slope IBP (lower). The pressure flow index and impedance ratio, particularly in the distal esophagus, were higher with increasing viscosity and lower with increasing volume. IRP4s was higher for solids compared to liquids and viscous and higher in relation to volume for liquids only (Table 1).

The Relationship between Intrabolus Pressure and Peak Pressure Amplitude

Based on a previous observation that the intrabolus pressure at nadir impedance (PNadImp) correlated with esophageal peak pressure (7), we investigated the impact of bolus viscosity and volume on this correlation. For measurements of the whole esophagus, we observed that esophageal function in response to boluses of larger volume and more viscous consistency revealed a positive correlation between PNadImp and esophageal peak pressure (Spearman Rank correlations were significant for 5ml viscous $r = 0.487$, $p<0.05$, 10ml viscous $r = 0.669$, $p<0.005$, 2cm solid $r = 0.544$, $p<0.05$ and 4cm solid $r = 0.618$, $p<0.005$). When we examined the proximal and distal esophageal segments separately, this correlation was only present in the distal esophagus (correlations for proximal vs. distal esophagus respectively were $r = 0.244$, $p=0.224$ vs. $r = 0.698$, $p<0.001$ for 10m viscous and $r = 0.405$, $p=0.07$ vs. $r = 0.561$, $p<0.05$ for 4cm solid).

Perception of solid bolus passage

The subjective perception of bolus transit was most frequently reported during swallowing of solids. Ten of our subjects reported some perception of bolus passage during at least one solid swallow. Five subjects reported a maximum perception score of 2 (i.e. ‘awareness’ of normal bolus passage) whilst five reported maximum scores of 3-

6 consistent with the subjective perception of bolus hold up (mean score 4). Grouping of subjects based upon levels of solid bolus perception revealed a significantly higher distal IBP slope in the subjects who reported maximum scores of 3-6 (Figured 3E). Other individual pressure-flow metrics did not achieve statistical significance for this grouped analysis, however IBP and TNadImp to PeakP, the other two metrics which are incorporated in the PFI calculation, were numerically higher (Figure 3 D) and shorter (Figure 3 F) respectively and this had the net effect of further amplifying the PFI overall (Figure 3 G). The impedance ratio was higher in some individuals suggesting ineffective clearance on a single swallow (see example impedance ratio plots from subjects without and with perception of bolus passage in Figure 2), however the impedance ratio was not higher in relation bolus perception overall (Figure 3 H). The size of peristaltic breaks (Figure 3 A) and IRP4s were also not significantly different in relation to bolus perception.

Discussion

In this study we explored the impact of bolus volume and bolus type on metrics descriptive of esophageal function as derived by AIM pressure-flow analysis in control subjects. In addition, we observed the swallowing of high volume and/or higher viscosity boluses reveals a positive relationship between distal intrabolus pressure and esophageal peak pressure. Finally, we report that the perception of bolus transit is associated with a higher rate of bolus pressurisation.

Our first observations relate bolus characteristics to the distance a bolus is propelled by pharyngeal swallow alone. Whilst a previous study has investigated the temporal distribution and pattern of clearance for a bolus in relation to pharyngeal propulsion using scintigraphy (11), in our assessment we utilised impedance measurements via calculation of the flow stasis point from the bolus trajectory curve (based on the timing of nadir impedance). We put forward that the position of the flow stasis point corresponds to the spatial location of *switch* from pharyngeal driven to esophageal peristalsis driven bolus transport (7). Increasing bolus viscosity resulted in the flow stasis point being located more proximally. Hence, a viscous bolus that is more resistant to movement and therefore harder to propel is not carried as far by pharyngeal propulsion. This places greater demands on esophageal peristalsis to transport the bolus over a longer distance from the point of stasis to EGJ, increasing the likelihood of transport failure in relation to the presence of peristaltic breaks.

Another interesting finding emerging from this study was the relationship between higher intrabolus pressures recorded when the lumen is maximally full with accumulated bolus (pressure at nadir impedance) and higher esophageal contractile pressure (peak pressure) amongst study subjects. The relationship was demonstrable with viscous and solid challenges only, and higher volumes demonstrated greater statistical confidence, therefore requiring bolus challenges not routinely used in clinical manometry testing (i.e. 5ml liquid). A similar relationship has been previously described in response to the outlet flow resistance produced following fundoplication surgery (12, 13); however in this study no obstruction was present. In the non-obstructed EGJ setting, peak pressures should not determine intrabolus pressures because pressure peak generation is located above the intrabolus pressure domain (14, 15). Hence our observation suggests that higher peak pressures may be occurring *in response to* higher intrabolus pressures, specifically those pressures which correspond to the lumen being maximally full.

The observation that muscle tension during peristaltic contraction is coupled to physical characteristics of the bolus being transported is not new. The exploration of such phenomena has been a major focus of past studies and it is generally accepted that there are two possible explanations for this relationship. Firstly, smooth muscle will contract more forcefully in circumstance of increased muscle length-tension prior to contraction, called 'pre-load' (e.g. larger volumes which fill the lumen more increase pre-load and therefore greater contractile force is generated), as well as during contraction onset, called 'after-load' (heavier more solid consistencies which are harder to empty increase after-load and therefore greater contractile force is generated) (16). The second explanation for a correlation between intrabolus pressure and peak pressure is that the presence of a bolus may stimulate local stretch receptors, modulating peristalsis via an intrinsic reflex. As demonstrated by Dodds and colleagues (18), bolus swallows, compared to dry swallows, produce higher peak pressures, longer contraction durations and a slower rate of progression of the peristaltic pressure wave and these effects are more pronounced in the distal esophagus. Similar findings were described more recently for viscous swallows in comparison to liquid swallows when using combined manometry and impedance (19). Ren and Schulze-Delrieu (20) also made similar observations in relation to peristalsis in the isolated opossum esophagus following the application of radial stretch by balloon distension or with weights. Whilst the initiation of primary peristalsis occurs via a central pathway and, by definition, pharyngeal swallow is essential for it to occur in vivo; normal esophageal functioning may also rely upon secondary compensatory mechanisms which regulate peristalsis whilst in progress, compensating for the increased demands of higher volume and greater solid consistency boluses by augmenting descending inhibition (facilitating bolus passage) and in turn, ascending excitation (facilitating bolus clearance). In relation to the existence of such mechanisms, we also note the descending esophageal peristaltic reflex in the opossum described by Patterson and colleagues (20) and the intrinsic wave of descending inhibition that precedes contraction of the distal esophagus, recently described in human subjects by Abrahao and colleagues (21).

An interesting new finding in this study was the relationship between altered pressure-flow metrics and bolus perception. Perception of bolus passage was reported by half of the subjects and this was almost always in relation to solids. In this case we are examining sub-clinical levels of bolus perception that clearly are not troublesome (healthy controls with nil dysphagia). Nevertheless, in a controlled laboratory setting, the subjects were able to report levels of bolus perception which appeared to correlate with increased bolus pressurisation (higher PFI).

The impedance ratio, relating nadir impedance to peak pressure impedance, is a new AIM analysis metric that may have diagnostic relevance as a single measure elevated in relation to ineffective bolus clearance. A higher ratio correlates with failed bolus clearance as determined by conventional impedance analysis (whereby each channel is individually analysed for clearance failure based on prolonged bolus clearance time at one or more sites) (9). Being a continuous measure rather than based on the categorisation of complete bolus transport (or not), this new metric may also better reflect the extent of bolus clearance failure.

The pressure flow index calculation, based on multiple AIM metrics, is an attempt to allow the multifactorial causes of dysphagia symptoms to be embodied in a single predictor. This index captures the cumulative effects of subtle differences in the individual metrics. The PFI was developed in the setting of predicting post-fundoplication dysphagia (4, 5). In essence, the PFI reflects flow resistance/bolus pressurisation as the bolus passes through the distal esophagus towards and through the esophago-gastric junction. Reduced speed of bolus movement, reduced diameter/luminal relaxation and/or reduced EGJ opening should, in theory, increase the PFI. We have previously demonstrated that patients with non-obstructive dysphagia have an elevated PFI compared to controls; this is driven by differences in all three PFI variables (*shorter* TNadImp to PeakP, *higher* median IBP and IBP slope (6)). Of these key metrics, higher IBP slope was the only one significantly altered in relation to perception in the current study; being higher in subjects who reported more intense perception of bolus transit. IBP slope is a complex metric and was designed to quantify the rate of pressure change during transition from a full lumen to an occluded lumen. Further studies combined with fluoroscopy are needed to better understand this and the other metrics we measure with our method.

Heightened bolus perception was not associated with standard HRM metrics, such as isocontour defect size or higher IRP4s, and neither was the impedance ratio significantly altered in relation to bolus perception. Together these observations suggest that factors such as weak peristalsis, EGJ resistance and/or ineffective bolus clearance are not responsible for inducing bolus transit perception. This study is however based on normal subjects and further HRIM investigations with our new analysis approach need to be undertaken in patients with dysphagia symptoms. Nevertheless, it should be recognised that the patterns of change in the different pressure-flow metrics, seen here in relation to bolus perception, are consistent with those previously described for dysphagia patients in previous pilot studies which utilised pressure-impedance measurements of low spatial resolution in conjunction with the administration of viscous boluses (4-6, 9).

In conclusion, we report that bolus volume and bolus viscosity impact esophageal function and thus alter AIM analysis metrics. More challenging high volume/heavy viscosity boluses, more akin to real life scenarios, reveal relationships between intrabolus pressures and esophageal peak pressures that suggest an active modulation of peristalsis during bolus transport. Finally, perception of bolus hold up was associated with AIM analysis pressure-flow metrics indicative of heightened bolus pressurisation during the phase of transition from a full lumen to an occluded lumen. These observations warrant further validation and exploration in patient populations reporting symptoms of dysphagia.

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Tables

	Volume 5ml/2cm			Volume 10ml/4cm		
	5ml Liquid	**5ml Viscous**	**2cm Solid**	**10ml Liquid**	**10ml Viscous**	**4cm Solid**
FSP position						
cm above EGJ	6 ± 1[bc]	10 ± 1[a]	11 ± 1[a]	6 ± 1[bc]	10 ± 1[a]	11 ± 1[a]
% eso length	27 ± 3[bc]	49 ± 3[a]	56 ± 4[a]	29 ± 4[bc]	48 ± 3[a]	55 ± 2[a]
Whole Esophagus						
IC Defect cm	0.4 [0.1, 1.3]	1.5 [0.2, 2.5]	0.7 [0.1, 2.6]	0.7 [0.1, 2.0]	0.3 [0.1, 0.3][#]	0.6 [0.1, 1.9]
Peak P mmHg	84 ± 7	77 ± 7[c]	87 ± 8[b]	77 ± 7[bc#]	87 ± 7[a#]	95 ± 7[a]
PNadImp mmHg	4 ± 0[bc]	7 ± 0[ac]	11 ± 1[ab]	5 [3, 6][bc#]	9 [7, 11][ac#]	16 [12, 21][ab#]
IBP mmHg	5 [4, 6][bc]	10 [8, 12][ac]	14 [11, 23][ab]	6 [4, 7][bc#]	12 [9, 14][ac#]	22 [16, 27][ab#]
IBP slope mmHg/s	6 ± 1[bc]	14 ± 1[ac]	25 ± 2[ab]	4 ± 0[bc#]	10 ± 1[ac#]	18 ± 2[ab]
TNadImp-PeakP s	3.9 ± 0.2[bc]	2.7 ± 0.1[a]	2.5 ± 0.1[a]	4.0 ± 0.2[bc]	2.9 ± 0.1[a#]	2.9 ± 0.1[a]
PFI	16 [7, 33][bc]	103 [71, 145][ac]	267 [160, 854][ab]	13 [5, 16][bc]	60 [46, 90][ac#]	190 [133, 434][ab]
NadImp/ImpPeakP	0.20 ± 0.02[bc]	0.31 ± 0.02[ac]	0.38 ± 0.03[ab]	0.14 ± 0.01[bc#]	0.24 ± 0.01[ac#]	0.35 ± 0.03[ab]
Prox. Esophagus						
Peak P mmHg	63 ± 4[c]	64 ± 4[c]	75 ± 5[ab]	61 [47, 78][bc]	72 [54, 83][ac #]	86 [72, 97][ab#]
PNadImp mmHg	0 ± 0[bc]	5 ± 0[ac]	10 ± 1[ab]	2 [0, 3][bc#]	8 [5, 10][ac#]	16 [10, 22][ab#]
IBP mmHg	3 ± 0[bc]	8 ± 1[ac]	16 ± 2[ab]	4 ± 1[bc#]	10 ± 1[ac#]	21 ± 2[ab#]
IBP slope mmHg/s	15 ± 1[bc]	23 ± 2[ac]	37 ± 4[ab]	11 ± 1[bc#]	16 ± 2[ac#]	28 ± 3[ab#]
TNadImp-PeakP s	2.0 ± 0.1[bc]	1.7 ± 0.1[ac]	1.6 ± 0.1[ab]	2.0 [1.7, 2.2][b]	1.7 [1.5, 2.2][a#]	1.9 [1.6, 2.3]
PFI	27 [10, 78][cb]	185 [79, 246][a]	454 [242, 1132][a]	22 [13, 55][bc]	91 [55, 186][ac]	370 [190, 1024][ab]
NadImp/ImpPeakP	0.22 ± 0.02[bc]	0.30 ± 0.02[ac]	0.36 ± 0.03[ab]	0.17 ± 0.01[bc#]	0.23 ± 0.01[ac#]	0.29 ± 0.03[ab#]
Dist. Esophagus						
Peak P mmHg	92 ± 9	82 ± 10	91 ± 10	82 ± 9[c#]	94 ± 9[#]	100 ± 8[a#]
PNadImp mmHg	5 [3, 6][bc]	8 [6, 10][a]	9 [7, 16][a]	6 [4, 7][bc#]	10 [7, 12][ac#]	17 [12, 20][ab#]
IBP mmHg	5 [4, 7][bc]	11 [7, 14][ac]	16 [10, 26][ab]	7 [4, 8][bc#]	13 [10, 15][ac#]	22 [16, 26][ab#]
IBP slope mmHg/s	3 ± 0[bc]	11 ± 2[ac]	20 ± 3[ab]	1 [1, 2][bc#]	8 [4, 11][ac#]	12 [7, 20][ab#]
TNadImp-PeakP s	4.7 ± 0.2[bc]	3.1 ± 0.1[a]	2.9 ± 0.2[a]	4.9 ± 0.2[bc]	3.3 ± 0.1[a#]	3.2 ± 0.2[a#]
PFI	5 [2, 17][bc]	58 [20, 99][ac]	148 [92, 623][ab]	3 [1, 15][bc#]	40 [14, 66][ac#]	126 [70, 295][ab]
NadImp/ImpPeakP	0.19 ± 0.02[bc]	0.31 ± 0.02[ac]	0.39 ± 0.03[ab]	0.13 ± 0.01[bc#]	0.24 ± 0.01[ac#]	0.37 ± 0.04[ab]
EGJ						
IRP4s mmHg	2 ± 1[c]	3 ± 1	4 ± 1[a]	3 ± 1[c#]	3 ± 1[c]	4 ± 1[ab]
Nadir P mmHg	0 [-1, 0]	0 [-1, 1]	0 [0, 1]	0 [-1, 1][#]	0 [-1, 0]	0 [0, 2]

Table 1. Effects of Bolus type and volume on analysis metrics. Data are presented as mean ± SEM or median [IQR].

[abc] Bolus type different for specific volume using One Way Repeated Measures Analysis of Variance or Friedman Repeated Measures Analysis of Variance on Ranks and Pairwise Multiple Comparison Procedures (Holm-Sidak method or Tukey Test);

[a]significantly different to liquid, [b]significantly different to viscous, [c] significantly different to solid.

#significant effect of volume for equivalent bolus type by paired t-test or Wilcoxon Signed Rank test.

Figure Legends

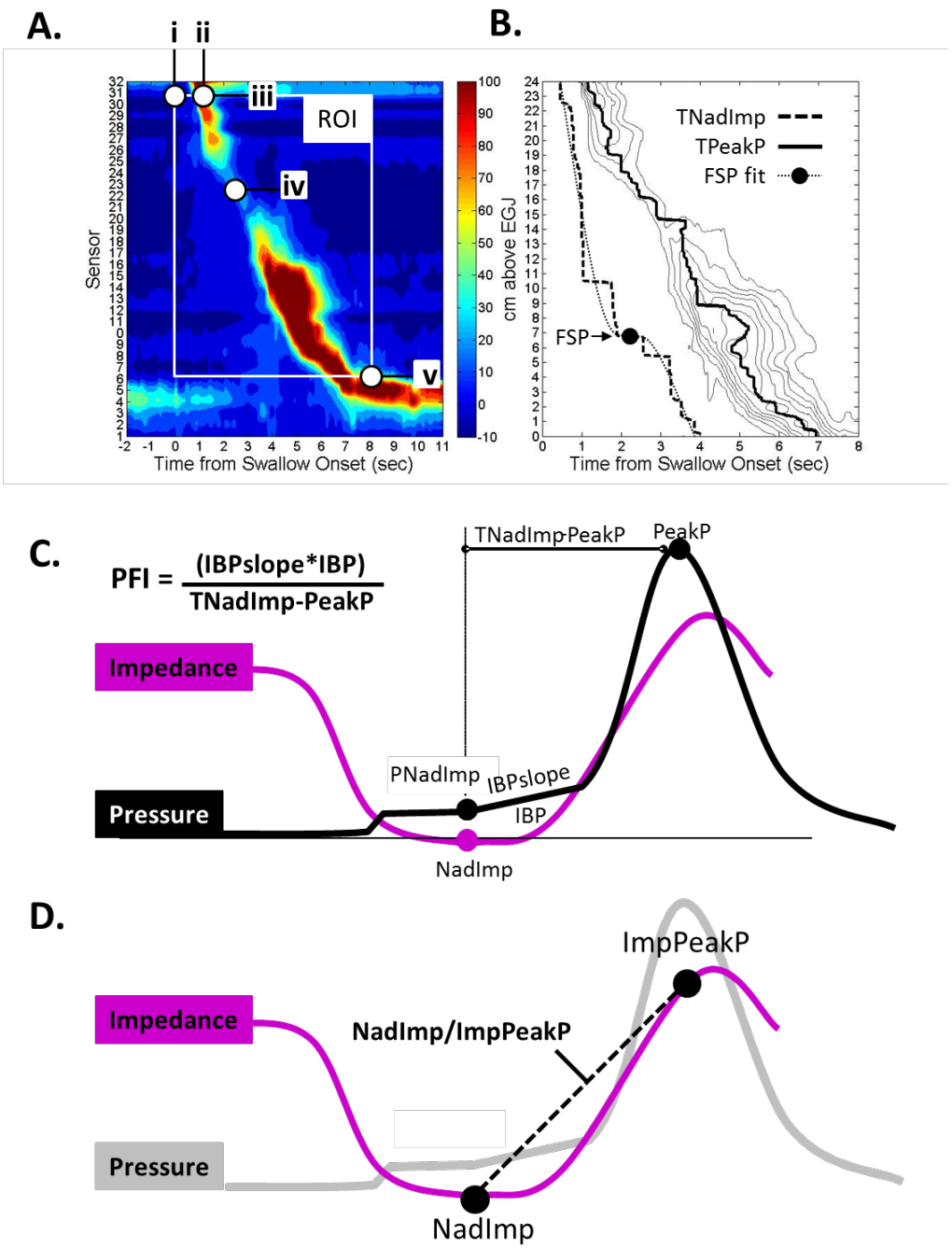

Figure 1. **Esophageal AIM analysis. A.** An esophageal pressure topography plot showing pressures associated with a 5ml liquid bolus swallow. Five space-time landmarks define the region of interest (ROI) for calculations (i. the time of onset of swallow; ii. the time of proximal peak pressure; iii. the proximal margin of the esophageal pressure wave sequence; iv. the position of the transition zone; v. distal margin of the esophageal pressure wave sequence). **B.** A pressure contour plot of the ROI in A. showing the bolus trajectory pathway and flow stasis point (FSP) defined using the time of nadir impedance (TNadImp). This identifies bolus passage relative to the esophageal pressure wave (time of peak pressure, TPeakP). **C.** Derivation of the AIM analysis metrics and the pressure flow index (PFI) from esophageal impedance and pressure recordings. Guided by the timing of landmarks Nadir Impedance and Peak Pressure, the AIM metrics are measured along the esophageal ROI using an automated software algorithm. **D.** Derivation of impedance ratio based on the nadir impedance (NadImp) and peak pressure impedance (ImpPeakP) (refer also to Figure 2).

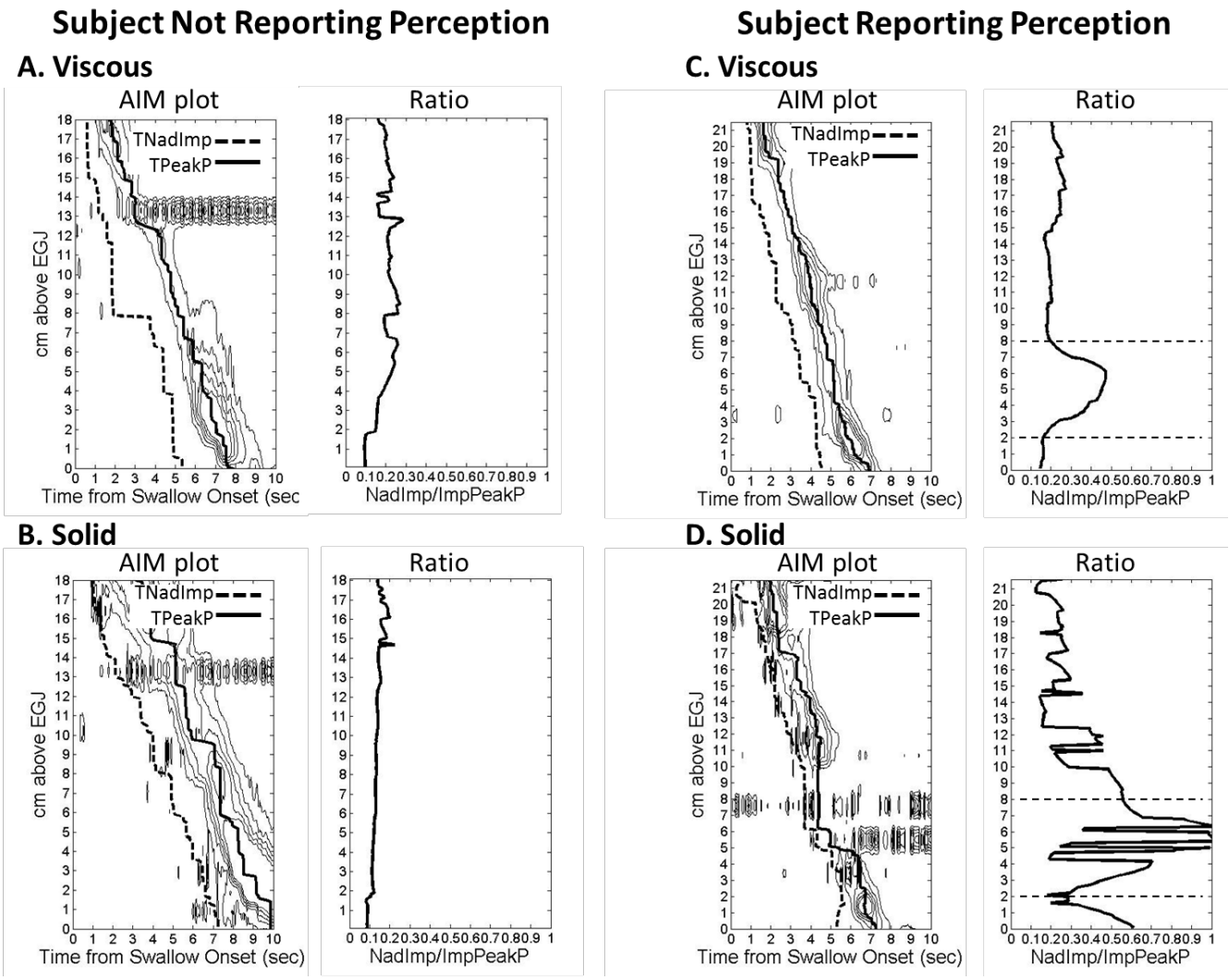

Figure 2. Calculation of the Impedance ratio along the esophagus. Example viscous and solid swallows are shown from a subject who reports no-bolus bolus perception (A and B) and a subject who perceives bolus passage for solids (C and D). AIM plots (left) show pressure contour plots (with iso-contours starting at 20mmHg) with time of nadir impedance (TNadImp) and time of peak pressure (TPeakP) superimposed. Graphs (right) show the impedance ratio. **Notes:** The subject with bolus perception reported bolus stepwise or slow passage during the solid swallow suggesting that some stasis had occurred. For this subject both viscous and solid swallows (C and D) demonstrate a focal region of higher impedance ratio in the distal esophagus between 2-8cm above the EGJ (this region is demarcated in graphs right by horizontal dotted lines). In the case of the solid swallow (D) a peristaltic break is also visible within this region, which would be compatible with incomplete bolus transit.

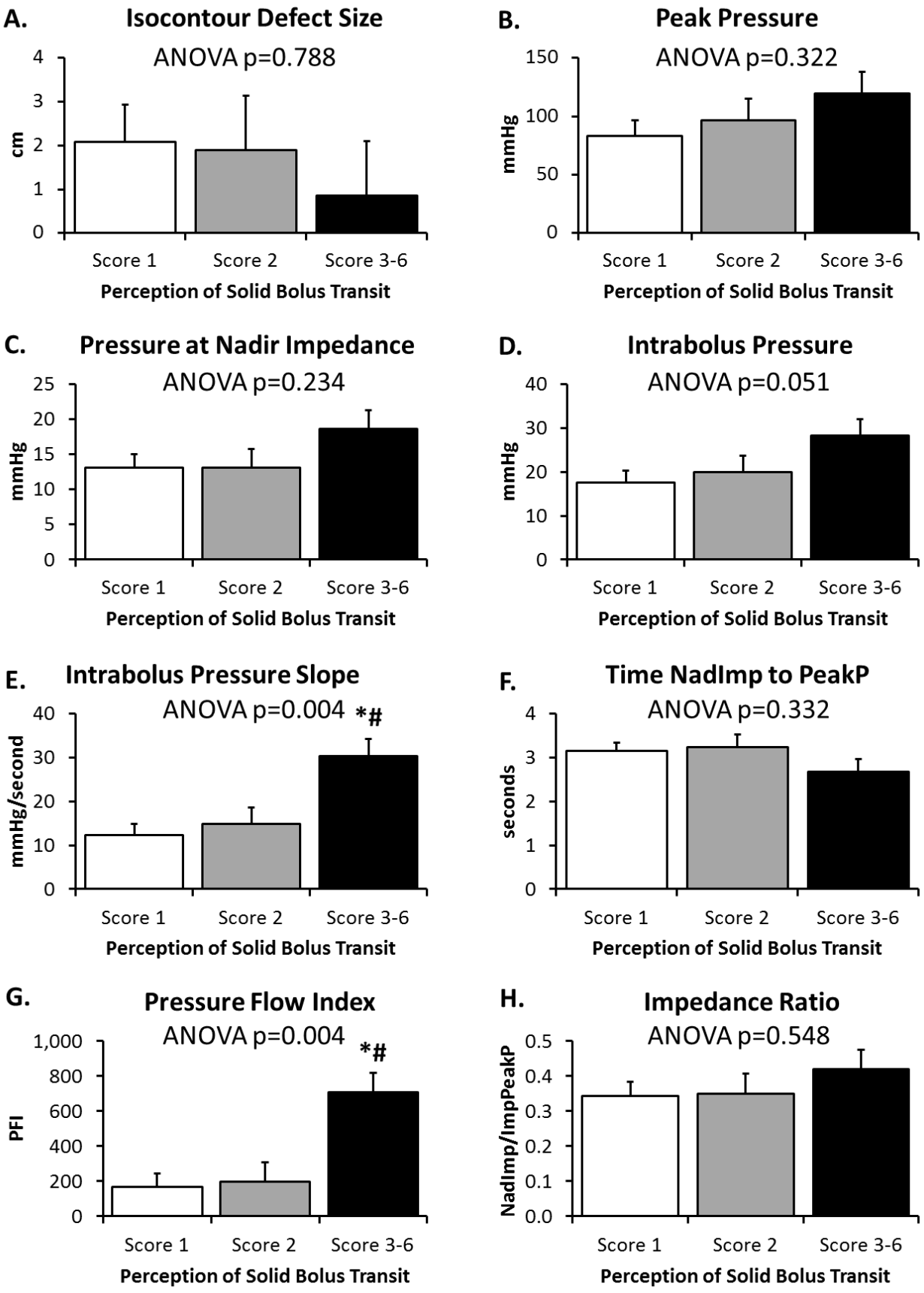

Figure 3. Results for main pressure-flow metrics derived for solid boluses in subjects grouped in relation to the perception of solid bolus transit. Data are expressed as least square means ± SE. P-values are for ANOVA allowing for effects of differences in the two acquisition systems used. *# indicates pairwise statistical significance (Holm-Sidak method) vs. Score 1(*) and Score 2(#).