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New Insights into Pharyngo-Esophageal Bolus Transport Revealed by Pressure-Impedance Measurement

T Omari[1,2]

S Kritas[1]

C Cock[3]

Author Affiliations:

[1]Gastroenterology Unit, Women's and Children's Health Network, Adelaide

[2]School of Paediatrics and Reproductive Health, University of Adelaide

[3]Gastrointestinal Motility Unit, Repatriation General Hospital, Adelaide

Author for correspondence:

Taher Omari, PhD

NH&MRC Senior Research Fellow

Gastroenterology Unit, Women's and Children's Health Network

72 King William Rd, North Adelaide SA 5006 South Australia

Email: taher.omari@adelaide.edu.au

Abbreviations:

AIM	automated impedance manometry
Zn	nadir impedance
TZn	time of nadir impedance
PZn	pressure at nadir impedance
TNadImp-PeakP	time of nadir impedance to peak pressure
iZn/Z	integrated Zn/Z ratio
FSP	flow stasis point
IRP4s	integrated four second relaxation pressure
20mmHg IC defect	20mmHg isocontour defect

Abstract

Introduction: Pharyngeal propulsion, strength of peristalsis and esophago-gastric junction (EJG) resistance are determinants of esophageal bolus transport. This study used pressure-impedance methods to correlate pharyngo-esophageal function with the esophageal bolus trajectory pathway and pressures generated during bolus transport.

Methods: Pharyngo-esophageal pressure-impedance measurements were performed in 20 healthy adult controls. Pharyngeal automated impedance manometry was performed to derive pharyngeal swallow function variables. The esophageal time of nadir impedance (TZn) was used to track bolus trajectory pathway. The inflexion, or flow stasis point (FSP), of the trajectory curve was determined as were the pressures within the bolus (PZn) above and below the FSP. The size of 20mmHg isocontour defect measured the integrity of the peristaltic wave.

Results: For viscous boluses, weaker pharyngeal bolus propulsion correlated with the FSP being located higher in the esophagus. Pressure within the bolus was observed to increase at the FSP and below the FSP in a manner that correlated with the magnitude of esophageal peak pressures. Larger 20mmHg isocontour defects were associated with lower pressures within the bolus at the FSP and below.

Conclusion: The FSP of the bolus trajectory pathway appears to represent a switch from bolus propulsion due to pharyngeal mechanisms to bolus propulsion due to esophageal mechanisms. 20mmHg isocontour defects significantly reduce bolus driving pressure at or below the FSP.

(215 words)

Introduction:

Bolus transport from mouth to stomach relies on esophageal peristalsis and thus can be impeded by disordered/defective peristalsis and/or abnormally high esophago-gastric junction (EGJ) pressures (1-6). Pharyngeal propulsion also has an important role, as swallowing force alone can propel boluses significant distances along the length of the esophagus. This aspect of swallowing physiology is however difficult to measure with pressure alone and therefore is largely ignored in the context of the potential assistance pharyngeal propulsion may give to bolus transport.

Current understanding of human esophageal function in relation to bolus swallowing is largely based on pressure measurements performed concurrently with fluoroscopic imaging. In recent years the technology for pressure measurement has evolved considerably, and this has advanced clinical use of manometric methods and has led to the development of a unified high-resolution solid state manometry-based classification system for recognition of esophageal and EGJ dysfunction (1, 2).

Combined pressure and impedance recording within the lumen of the esophagus offers the potential to non-radiologically measure the dynamics of bolus transport in relation to the pressures driving it. Recently, we developed a novel automated impedance manometry method (called AIM analysis) to better describe the interactions between bolus transport and pressure generation within the pharynx (7-9). The keystone of this novel approach is the identification of the timing of nadir impedance which can be used to track the trajectory of passage of the centre of the bolus relative to the time of pressure generation. In this pilot study we used a similar technique to assess the trajectory of bolus passage in the esophagus and examined the relationship between the bolus trajectory pathway and pharyngo-esophageal bolus transport

mechanisms. We hypothesised that pharyngeal forces are an important factor determining the trajectory and projection of the bolus head into the esophagus.

Methods:

Subjects and Protocol

The study protocol was approved by the Southern Adelaide Clinical Human Research Ethics Committee and performed at Repatriation General Hospital, Daw Park, Adelaide. Twenty subjects (8 males, mean age 31±2 yrs, age range 21-48 yrs) underwent pharyngo-esophageal manometry and impedance studies. All subjects were screened to assess difficulty with swallowing a range of foods using a validated dysphagia composite score (10). All reported no dysphagia symptoms (Score of 0 out of 45). A 3.2mm diameter solid state manometric and impedance catheter incorporating 25 1cm-spaced pressure sensors and 12 adjoining impedance segments, each of 2 cm (Unisensor USA Inc, Portsmouth, NH) was used. Pressure and impedance data were acquired at 20Hz (Solar GI acquisition system, MMS, The Netherlands). Subjects were intubated after application of topical anaesthesia (lignocaine spray) to the naso-pharynx and studied sitting upright. The pressure-impedance sensor array was not large enough to accommodate the entire region from velo-pharynx to EGJ, therefore the catheter was positioned in the first instance with sensors straddling the region proximal of the transition zone to stomach. After a 10min accommodation period, subjects were then tested with 5x5ml and 5x10ml of saline liquid boluses and then with identical volumes of a standardised viscous bolus medium (viscosity 450K cPs, supplied by Sandhill Scientific, Highlands Ranch, Denver USA). The catheter was then re-positioned with sensors straddling the region from velo-pharynx to proximal esophagus and test swallows repeated for the assessment of pharyngeal function.

Pharyngeal AIM Analysis

Pharyngeal AIM analysis of impedance-manometry text data files was performed to derive pharyngeal swallow function variables. The variables and their functional meaning are described in Table 1 and the method for derivation of these variables and validation has been described elsewhere (7-9).

Esophageal Analysis

For this study the esophageal analysis focused upon using the time of nadir impedance (TZn) during bolus swallow to track the trajectory pathway of the bolus head as it moves down the esophagus (Figure 1 A and B). Using the individual TZn curves for recorded swallows (Figure 1 C) the mean TZn curve was determined. Typically the TZn curve shows the bolus flowing rapidly, followed by deceleration and then acceleration again as the bolus approaches the EGJ. We hypothesised that the position of flow 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 time and position of flow stasis, called the *flow stasis point* (FSP) was objectively determined from the mean TZn curve using the point of inflexion of a 3rd order polynomial best fit curve (Figure 1 D). The position of the FSP was standardised relative to esophageal length which was defined as the distance from UES distal margin to EGJ proximal margin measured during peristalsis.

In addition, the pressures at nadir impedance (PZn) were used as a measure of the pressure within the bolus above the FSP (deceleration), at the FSP (stasis) and below the FSP (acceleration). Peristaltic wave pressures were assessed using the average peak pressure measured for the region proximal of the transition zone and the distal region from transition zone to EGJ. The overall integrity of the peristaltic wave was assessed by measuring extent of the peristaltic wave with peak pressures <20mmHg (called the 20mmHg isocontour defect or 20mmHg IC defect) (3, 4). The

extent of EGJ relaxation was assessed using the average minimal integrated relaxation pressure for a 4-s interval or 4 sec integrated relaxation pressure (IRP4s) (11).

Statistics

The primary analysis examined the relationship between average esophageal and pharyngeal function variables determined for all swallows and the position of the FSP using Pearson's correlation. Effects of bolus type on functional variables were compared with Two Way Repeated Measures ANOVA allowing for bolus volume effects. The effects of peristaltic defect size were assessed using One Way Analysis of Variance with pairwise multiple comparison procedures.

Results

Effect of bolus type

Based upon TZn curves, the estimated time from swallow to bolus reaching the EGJ was 3.3±0.2sec on average for liquid boluses and 4.7±0.3sec for viscous boluses ($p<0.001$). Pharyngeal PZn, flow interval and iZn/Zratio were higher/longer and TNadImp-PeakP was shorter for viscous boluses compared to liquid (Table 2). Hence greater bolus viscosity increased pharyngeal intrabolus pressures and the degree of post-swallow residue. Esophageal 20mmHg IC Defect size was shorter and esophageal PZn was higher with viscous boluses (Table 2). Peak pressures recorded for the pharynx and esophagus were not different in relation to bolus type (Table 2).

Determinants of the position of the FSP

Based on the location of the FSP, liquid boluses were propelled further along the length of the esophageal lumen than viscous boluses (FSP above the EGJ 7±1 cm vs 12±1 cm respectively, $p<0.005$). The position of the FSP did not correlate with the position of the transition zone and was

located on average 8cm below the TZ for liquid and 3cm below for viscous. The time from swallow to FSP was 1.6±0.1sec for liquid and 1.7±0.2sec for viscous boluses (ns).

Table 3 shows the relationship between pharyngeal and esophageal variables and the position of the FSP. No significant correlations were observed with liquid boluses. However, for viscous boluses, *shorter* TNadImp-PeakP (Figure 2A), *longer* flow interval and *higher* iZn/Z (Figure 2B) significantly correlated with the FSP being located *higher* in the esophagus. Whilst within normal limits, these data correlate a weaker pharyngeal function with a higher FSP. Esophageal variables did not correlate with FSP position.

Determinants of pressure within the bolus

In order to address the hypothesis that the position of flow stasis represents a *switch* from bolus propulsion due to pharyngeal mechanisms to bolus propulsion due to esophageal mechanisms we examined the correlation of esophageal variables with PZn above the FSP, at the FSP and below the FSP (as per illustration in Figure 3A). For both liquid and viscous boluses, pressure within the bolus was observed to increase at positions below the FSP (Figure 3B). Correlation of esophageal variables and PZn at different axial positions relative to the FSP yielded a relationship between increased distal esophageal pressures and increased PZn. Significant correlations were observed between 3-4cm below the FSP for liquid boluses and FSP-2cm below for viscous boluses (Table 4). For viscous boluses, a correlation was observed between increased IRP4s (i.e. reduced EGJ relaxation) and increased PZn at 4-5cm distal to the FSP (Table 4). No esophageal variable correlated with PZn above the FSP.

Larger 20mmHg IC defect correlated with lower PZn at or below the FSP (liquid $r = -0.539$, $p<0.05$ at 3cm below FSP; viscous at FSP $r = -0.548$, $p<0.05$ and 1cm below $r = -0.466$, $p<0.05$). This

observation was explored further by comparing PZn for subjects with an average 20mmHg IC defect <2cm (i.e. complete peristaltic integrity, n=10) vs. those with average IC defect of moderate size (2-5cm, n=7) and large size (>5cm, n=3). The PZn for viscous boluses at FSP and 1cm below was significantly lower in subjects with moderate to large peristaltic defects (Figure 3C). There was no incremental difference apparent when comparing a defect size of 2-5cm vs. >5cm. The same observation was not reproduced with liquid boluses (Figure 3C) although a trend was observed when data for defect sizes 2-5cm and >5cm were combined ($p=0.077$ at 3cm distal to FSP).

Discussion

In this pilot study we employed novel methods of pressure impedance analysis to explore the role of pharyngeal swallow and esophageal peristalsis in determining bolus trajectory pathway and intrabolus pressure generation during bolus transport along the esophagus. Bolus trajectory pathway was measured in healthy subjects using the time of nadir impedance (TZn). TZn shows a typical trajectory curve with a pattern of bolus deceleration followed by stasis (inflexion) and then acceleration. Bolus trajectory pathway can be described mathematically and this allows the flow stasis point (FSP) to be determined objectively. Furthermore the pressure at TZn (i.e. PZn) measures the pressure within the bolus at maximum distension during bolus passage. Our findings demonstrate that pharyngeal mechanisms are an important determinant of the distance a bolus will travel before decelerating. However once the bolus slows down and reaches stasis, the pressure within the bolus appears to be linked to the amplitude of esophageal body contraction. Hence we provide evidence that esophageal body contractile amplitude may be *least* important prior to the FSP and *most* important after the FSP.

In this study we begin to discriminate the role of pharyngeal bolus propulsion as distinct from esophageal peristalsis. Ever since upper gastrointestinal motility has received the attention of

physiologists, pharyngeal propulsion, esophageal peristalsis and EGJ resistance have been recognised as working in concert; all being important for normal effective swallowing. Nevertheless pharyngeal and esophageal function are routinely treated as separate entities and very rarely assessed together in a meaningful way. In essence this is due to the lack of objective measures that link them. In this study we assessed pharyngeal function using AIM analysis variables and demonstrated a correlation between FSP position and bolus propulsion. Although within normal limits, the subjects who projected the bolus further had evidence of 'better' pharyngeal swallowing. This significant relationship between TNadImp-PeakP and FSP position was an inconsistent finding, only apparent with viscous boluses and with a low level of statistical confidence ($p=0.034$). However, the lack of an equivalent relationship with liquids may be explained by the fact the esophageal lumen is far less resistive to liquids allowing bolus trajectory pathway to be confounded by other factors such as gravity which can greatly assist distal movement of a bolus in circumstances when frictional forces are not large (13). Luminal diameter and the degree of descending inhibition may vary between subjects and this would alter the level of luminal resistance and the position of the FSP. It is also possible that, in performing pharyngeal and esophageal assessments during different sets of swallows, we introduced further variability to the dataset. Nevertheless, with no alternative evidence for the role of esophageal contraction in influencing the position of the FSP, we conclude that the shape of the bolus trajectory curve, from swallow onset to FSP is most likely driven by the active force of pharyngeal swallow but also influenced by relaxation due to descending inhibition, passive luminal frictional forces and gravity.

In our study we used PZn as a measure of pressures within the bolus. Whilst PZn is a hydrodynamic pressure synonymous with intrabolus pressure, we have purposefully not used these specific terms because PZn, whilst a hydrodynamic pressure, is measured at a fixed point in time and space that corresponds to the lumen achieving its maximum diameter (as indicated by

the nadir impedance). This is different to intrabolus pressure as currently applied, which is usually taken as the average/median pressure of the entire intrabolus domain. During the early part of the bolus trajectory curve (which we have called 'deceleration') PZn appears stable or gradually decreasing. During the latter part of the bolus trajectory curve (which we have called 'acceleration') PZn increases significantly as the bolus begins to move below the FSP. The pressurisation seen at the FSP and below is due to shortening of the intrabolus pressure domain as a consequence of peristalsis. At the FSP, the speed of bolus movement has slowed to stasis. With the bolus static, greater force is then needed to get the bolus moving again, and the bolus then gains momentum.

As subjects were studied upright, we cannot discount the potential for gravity also playing a role during the acceleration phase. In addition, the further increases in PZn at greater distances below the FSP are most likely influenced by the combined effects of continued shortening of the intrabolus domain and the degree of outlet flow resistance offered by the EGJ. The lack of a correlation between IRP4s and either the location of the FSP or magnitude of PZn, at or immediately below the FSP, suggests that EGJ resistance does not really influence the deceleration and stasis components of the bolus trajectory pathway (i.e. higher EGJ resistance does not cause the FSP to be located higher). It is possible for boluses, liquids in the upright position in particular, to be rapidly propelled the full length of the esophagus and make immediate contact with the EGJ, however measurements of FSP suggest that boluses for the most part slow down 7-12cm proximal of the EGJ even though the subjects were studied upright.

The 20mmHg IC defect is a key diagnostic parameter when assessing esophageal dysphagia using clinical high-resolution manometry (1-2). IC defects are particularly prevalent in the region of the transition zone and represent spatial separation of the proximal and distal contractile waves of the

esophagus and the loss of continuity of muscle squeeze is the major cause of bolus retention at the level of the transition zone (14). In patients with ineffective peristalsis leading to bolus retention, pressures within the bolus tail are significantly lower in the region of the transition zone (14). Consistent with these findings, we observed that PZn was *lower* at the FSP and below in subjects with moderate-severe IC defect compared to those without an IC defect. If esophageal peak pressures are too low, then the bolus tail is less well sealed and this can lead to retrograde escape/transport failure of the bolus, a marker of which is lower intrabolus pressures.

Our observations correlating higher PZn with higher peak esophageal pressures are interesting because it is well established that peak pressures cannot determine hydrodynamic pressures because peak pressure is only achieved at the location of maximal luminal occlusion, which is proximal to the bolus tail and therefore located *above* the intrabolus pressure domain (13, 16)). The simplest explanation for this correlation is that it is a consequential finding due to the fact that higher average peak pressures are invariably associated with a smaller IC defect. An alternative explanation is that higher intrabolus pressures lead to higher peak pressures via intrinsic neuroregulatory mechanisms that modulate peristalsis in relation to intrabolus pressure.

The objective and automated method of analysis is a strength of our measurement approach and allows, for example, bolus driving pressures to be very reliably determined. Traditionally in clinical practise, intra-bolus pressure has been measured with a view to assessing abnormally *high* pressures as an indirect marker of obstruction (i.e. high intrabolus pressures proximal to the EGJ or proximal to regions of esophageal narrowing such as stricture). We and others have linked *low* intrabolus pressures to defective (or weak) peristalsis and there may be potential diagnostic value in documenting low as well as abnormally high intrabolus pressures in relation to esophageal dysfunction.

Some of the insights we provide are not necessarily new and have previously been expounded others who have applied mechanical principles to the understanding of esophageal bolus transport mechanisms (13-17). The importance of our current findings lie however in our ability to describe the process of bolus transit using objectively measurable and automatically derived impedance-pressure variables, rather than the traditional method of pressure measurement combined with fluoroscopy. We also introduce what we believe are new metrics in relation to normal esophageal bolus transport; that being the location and pressure in relation to bolus stasis as demarcated by the timing and location of the FSP. Our data are suggestive that the FSP represents a *switch* from pharyngeal driven bolus transport to esophageal peristalsis driven bolus transport. However further evidence based on examination of, for example, posture effects and the effects of swallowing manoeuvres (e.g. effortful swallowing), are needed to prove this. Nevertheless we believe that our measurement method will allow easier delineation of the different roles of pharyngeal bolus propulsion and esophageal peristalsis (Figure 4).

Our subjects were mostly <40yrs and were screened for dysphagia, all being totally asymptomatic (score = 0). Nevertheless, half of our subject cohort had a moderate (>2cm, n=7) or severe (>5cm, n=3) IC defect. Hence an IC defect alone does not cause dysphagia symptoms even though it may reduce bolus pressurisation. How far the bolus is propelled into the esophagus in the first instance, may be an important determinant of the volume of bolus retailed in the esophagus in circumstances when bolus transport is ineffective. It may well be the case that the *closer* the FSP is to EGJ the *less* work peristalsis needs to do complete the task of bolus transport and the less volume of bolus residual retained, hence the impact of an IC defect may be ameliorated by stronger pharyngeal bolus propulsion in combination with an upright posture. This is the subject of ongoing research.

In conclusion, bolus flow along the esophageal lumen displays a typical bolus trajectory pathway characterised by bolus deceleration, stasis and then acceleration again. We present evidence that pharyngeal mechanisms determine the position of flow stasis whilst, at and below the flow stasis point, the integrity of esophageal body peristalsis, particularly in the region of the transition zone, determines the pressure within the bolus which may in turn regulate the magnitude of esophageal peak pressure in the distal esophagus. Defective esophageal peristalsis, even in asymptomatic individuals, can significantly reduce bolus driving pressures, however, it remains to be determined how these mechanisms are altered in relation to the perception of bolus hold up and the symptom of dysphagia.

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Funding, Competing interests

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Competing Interests:

Dr Omari holds a Patent Pending on AIM analysis methods.

Dr Omari is a technology consultant to Sandhill Scientific Inc.

Ms Kritas and Dr Cock have no competing interests.

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Description of Variable	What Variable Indicates
Pressure of the pharyngeal stripping wave	Pharyngeal contractile vigour. Abnormal = low
Pressure at the time of nadir impedance (PZn)	Pressure within the pharyngeal bolus Abnormal = high
Time from Nadir Impedance to Peak Pressure (TNadImp-PeakP)	Capacity to propel the bolus in advance of the pharyngeal stripping wave. Abnormal = short
Flow Interval	Bolus dwell time during swallow. Abnormal = long
Ratio of nadir impedance to post-swallow impedance (iZn/Z ratio)	Bolus residue Abnormal = high

Table 1. Description of pharyngeal variables used.

	Liquid	Viscous
Pharyngeal		
Peak Pressure mmHg	151±12	144±12
PZn	9±1	13±2**
TNadImp-PeakP msec	476±12	389±9***
Flow Interval msec	418±43	484±70*
iZn/Z ratio	82±12	138±20***
Esophageal		
20mmHg IC Defect cm	2.6±0.6	1.7±0.4*
Proximal peak pressure mmHg	34±4	55±5***
Distal peak pressure mmHg	68±8	72±7
Proximal PZn	3±1	10±1*
Distal PZn	5±0	8±0*
EGJ		
IRP4sec	6±1	6±1

Table 2. Average results for pharyngeal and esophageal variables. *Viscous significantly different to liquid allowing for effects of differences in volume using Two Way Repeated Measures ANOVA. *p<0.05, **p<0.01, ***p<0.005.

	Proximal Position of FSP (% Esophageal Length)	
	Liquid Bolus	**Viscous Bolus**
Pharyngeal		
Peak Pressure	0.285	0.119
PZn	0.159	-0.286
TNadImp-PeakP	0.301	-0.543*
Flow Interval	0.011	0.544*
iZn/Z ratio	0.018	0.645***
Esophageal		
20mmHg IC Defect	-0.324	-0.223
Proximal Peak Pressure	-0.113	0.183
Distal Peak pressure	0.352	0.316
Proximal PZn	0.327	0.014
Distal PZn	0.079	0.147
EGJ		
IRP4sec	0.001	0.065

Table 3. Pearson's Correlations (r) between average esophageal and pharyngeal function variables determined for all swallows and the position of the FSP. *Significant Correlation *p<0.05, **p<0.01,***p<0.005.

	Position where PZn was Measured										
	Proximal to FSP (cm)					*FSP*	*Distal to FSP (cm)*				
	5	*4*	*3*	*2*	*1*	*0*	*1*	*2*	*3*	*4*	*5*
Liquid Bolus											
Proximal peak pressure										[+]	
Distal peak pressure									+	+	
IRP4sec											
Viscous Bolus											
Proximal peak pressure											
Distal esophageal pressure						++	+++	[+]			
IRP4sec										[+]	+

Table 4. Correlation of esophageal peak pressure and IRP4s with the pressure within the bolus (PZn) at different axial positions relative to the FSP (as per Figure 3). + indicates significant correlation of higher PZn with higher esophageal peak pressure or higher EGJ relaxation pressures. Pearson's correlation p value [+] p=0.05-0.099, + p<0.05, ++ p<0.01, +++ p<0.005.

Figure 1. Esophageal analysis method.

A. A Clouse esophageal pressure topography plot of a bolus swallow showing pressures generated in the esophagus and EGJ.

B. The time of nadir impedance (TZn) during bolus swallow was used to track the trajectory pathway of the bolus head as it moves down the esophagus.

C. TZn curves for all recorded swallows.

D. The mean TZn curve. The time and position of the FSP was objectively determined using the point of inflexion of a 3^{rd} order polynomial best fit.

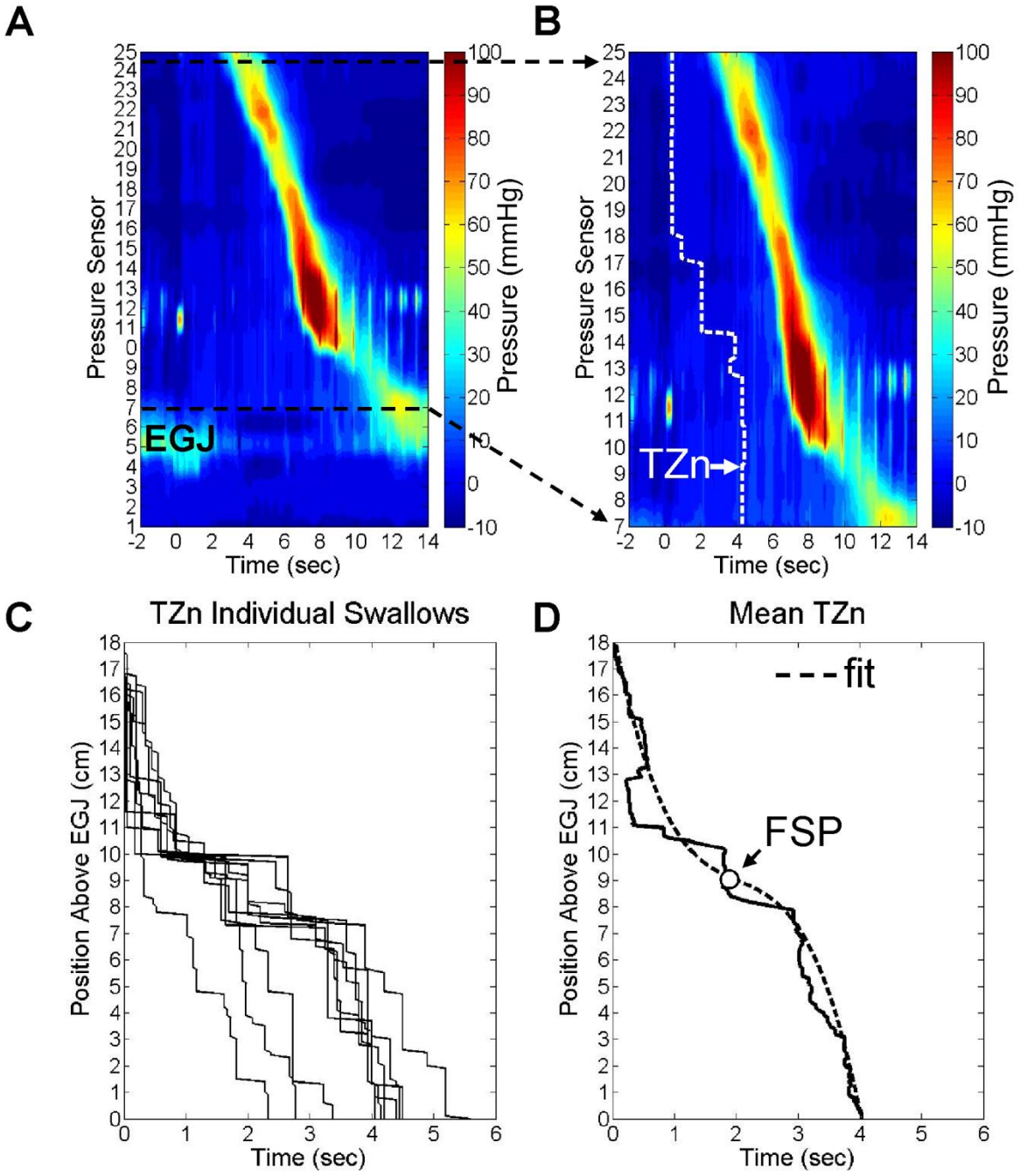

Figure 2. Correlations between the position of the FSP and (A) average TNadImp-PeakP and (B) average iZn/Z Ratio determined for viscous boluses. Pearson's Correlation r and p-values shown.

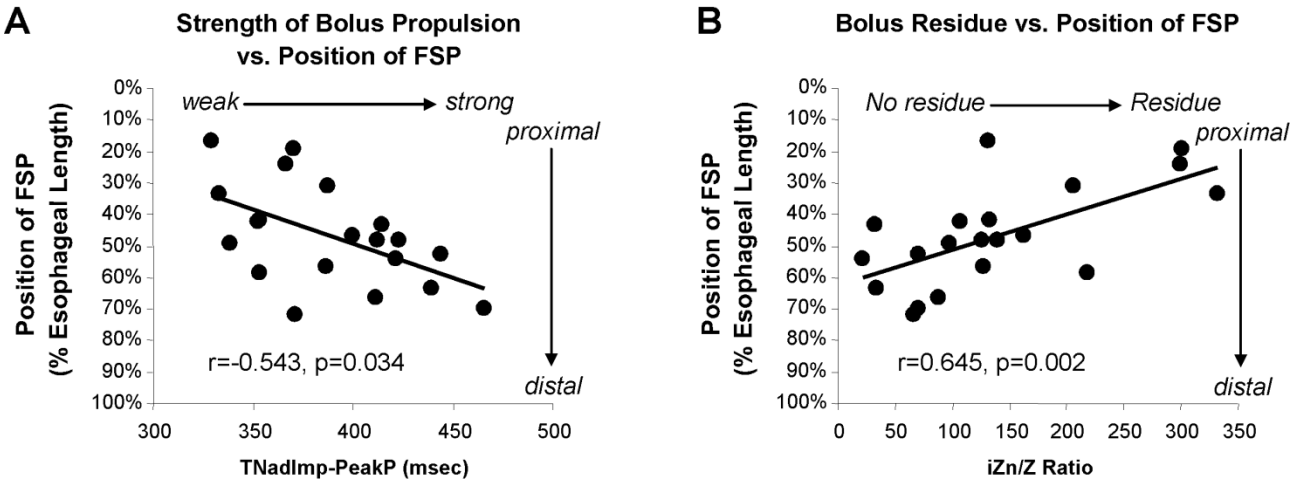

Figure 3. Measurement of pressure within bolus (PZn) at different axial positions relative to the FSP.

A. Example tracings showing where PZn was measured.

B. Average PZn for liquid and viscous boluses. Data are expressed as absolute pressure (top) and pressure relative to PZn at FSP (bottom).

C. Average PZn in relation to average size of 20mmHg IC defect. *p<0.05 across groups using One Way Analysis of Variance. #p<0.05 also for pairwise multiple comparisons vs. average defect <2cm.

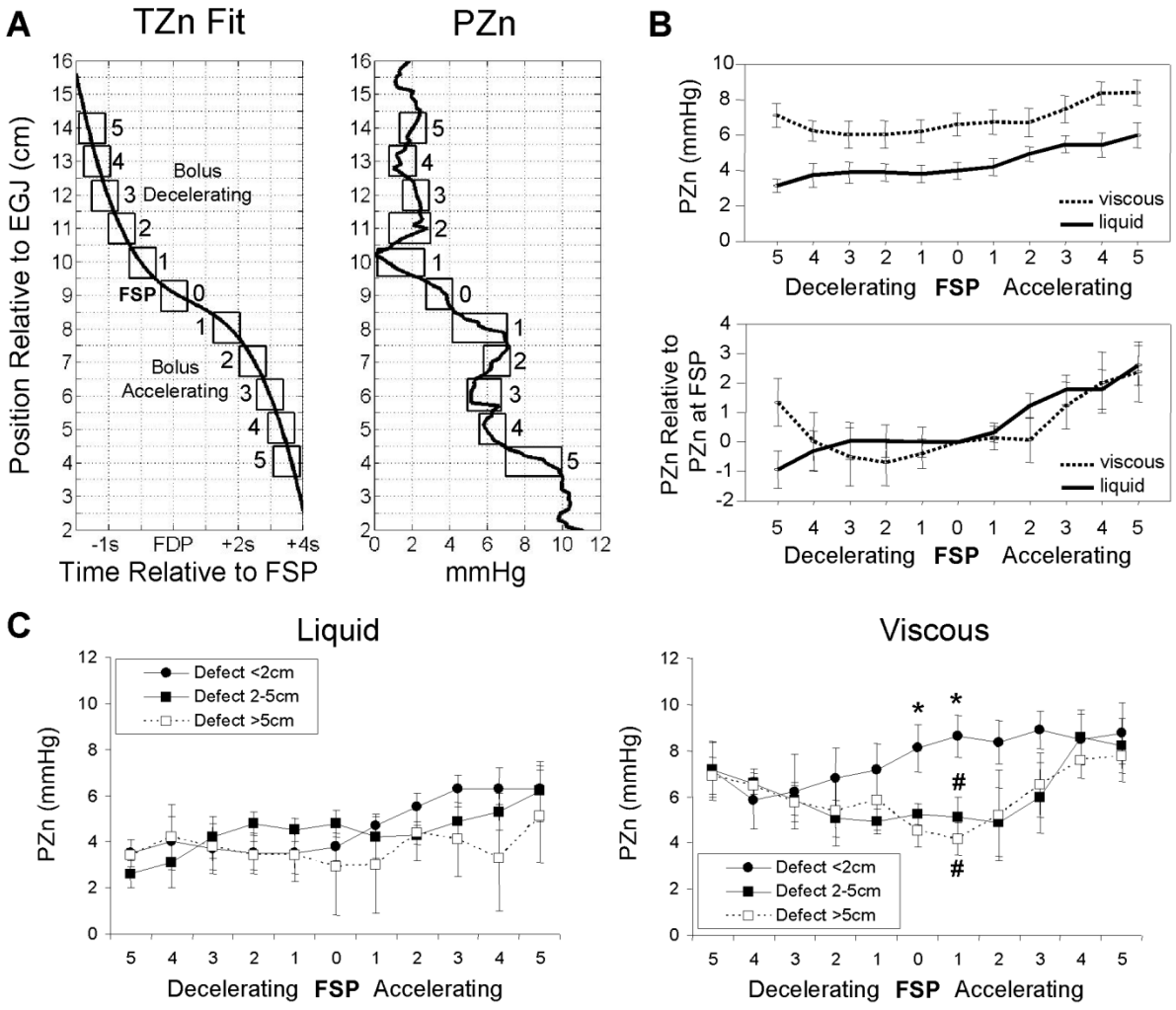

Figure 4. Determinants of bolus trajectory pathway and resultant intrabolus pressures.