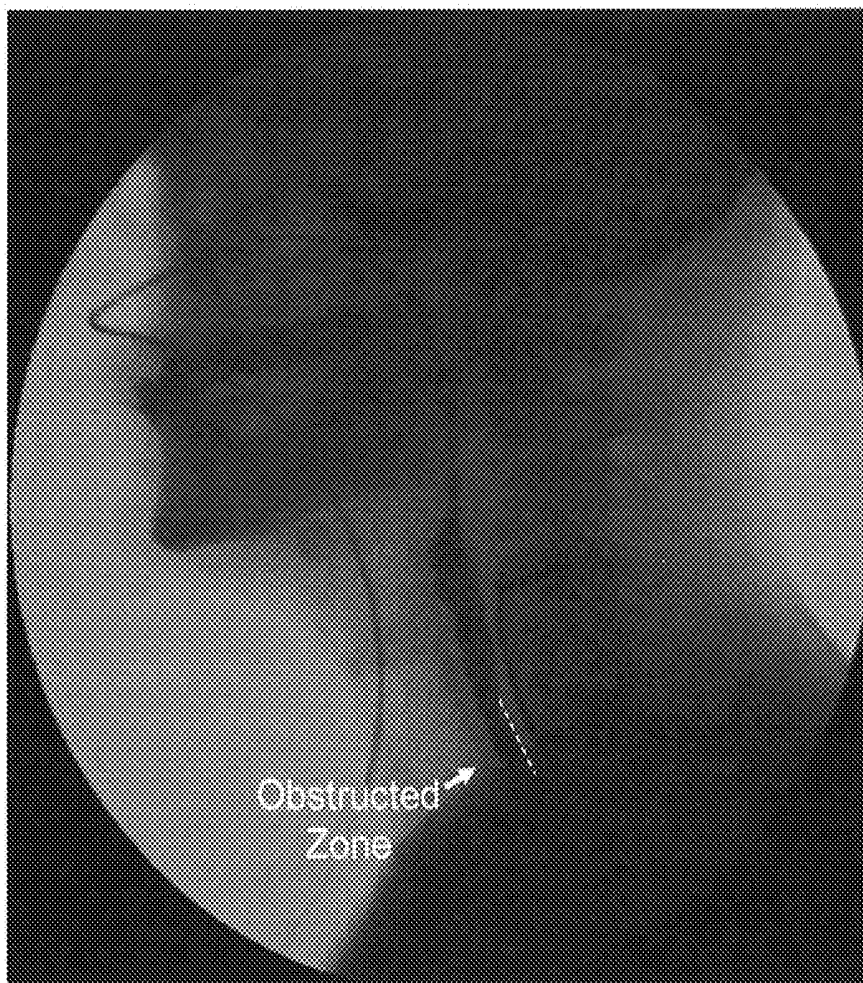




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(19) **United States**(12) **Patent Application Publication**
Omari et al.(10) **Pub. No.: US 2015/0073229 A1**(43) **Pub. Date: Mar. 12, 2015**(54) **SWALLOWING MOTOR FUNCTION
MEASUREMENT AND ASSESSMENT TOOLS,
METHODS, AND APPARATUS**(71) Applicants: **Taher Imad Omari**, North Adelaide
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(AU); **Nathalie Rommel**, Leuven (BE);
Jerry E. Mabary, Littleton, CO (US);
Thomas D. Stuebe, Littleton, CO (US)(21) Appl. No.: **13/897,294**(22) Filed: **May 17, 2013****Publication Classification**(51) **Int. Cl.**
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A61B 5/03 (2006.01)
A61B 5/053 (2006.01)(52) **U.S. Cl.**
CPC **A61B 5/4205** (2013.01); **A61B 5/053**
(2013.01); **A61B 5/037** (2013.01)
USPC **600/301**(57) **ABSTRACT**

Tools, methods and apparatus are provided that may be used to identify ineffective swallowing in the subject, including ineffective swallowing due to an obstruction, and may further be used to determine risk of aspiration in the subject. In one aspect, a method includes accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject. The method further includes combining and analyzing the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus on the subject. The swallowing motor function in the subject is assessed by comparing the value of the pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.



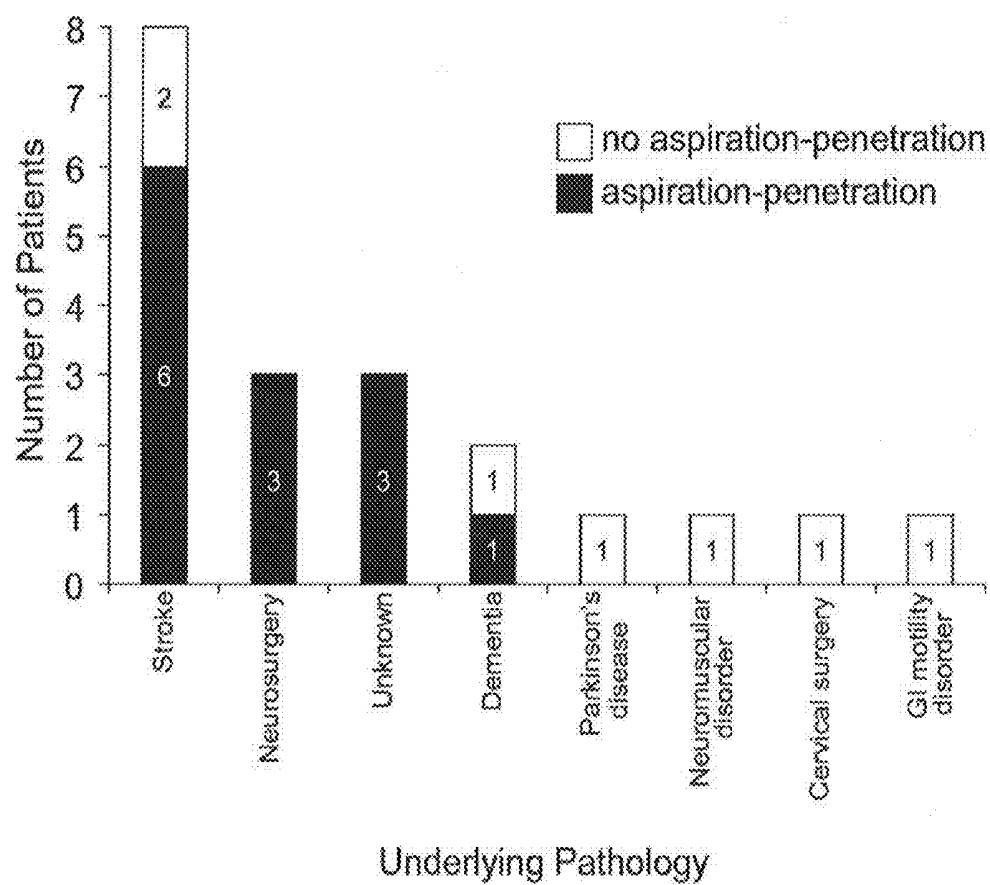
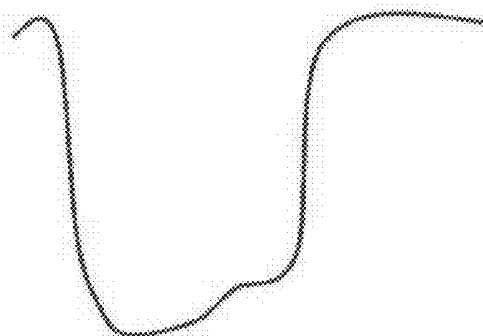
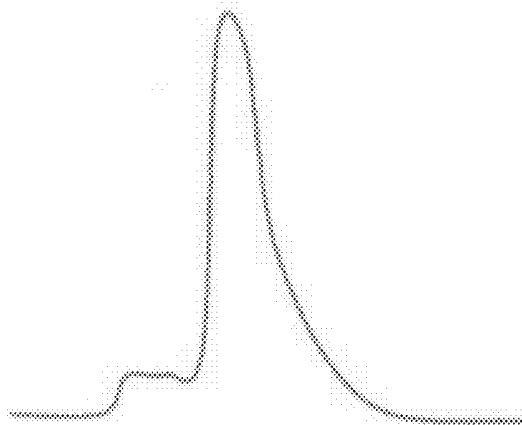
**FIGURE 1**

FIGURE 2

A



B



C

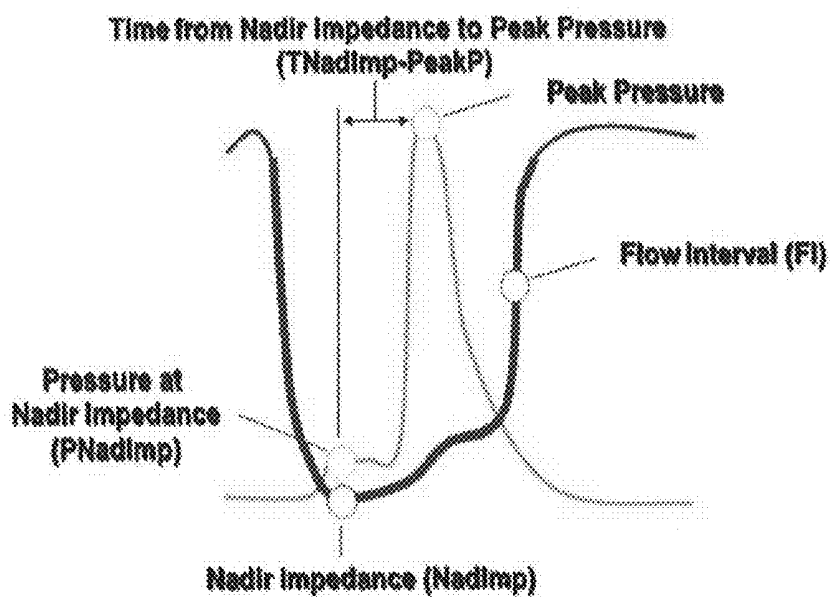


FIGURE 3

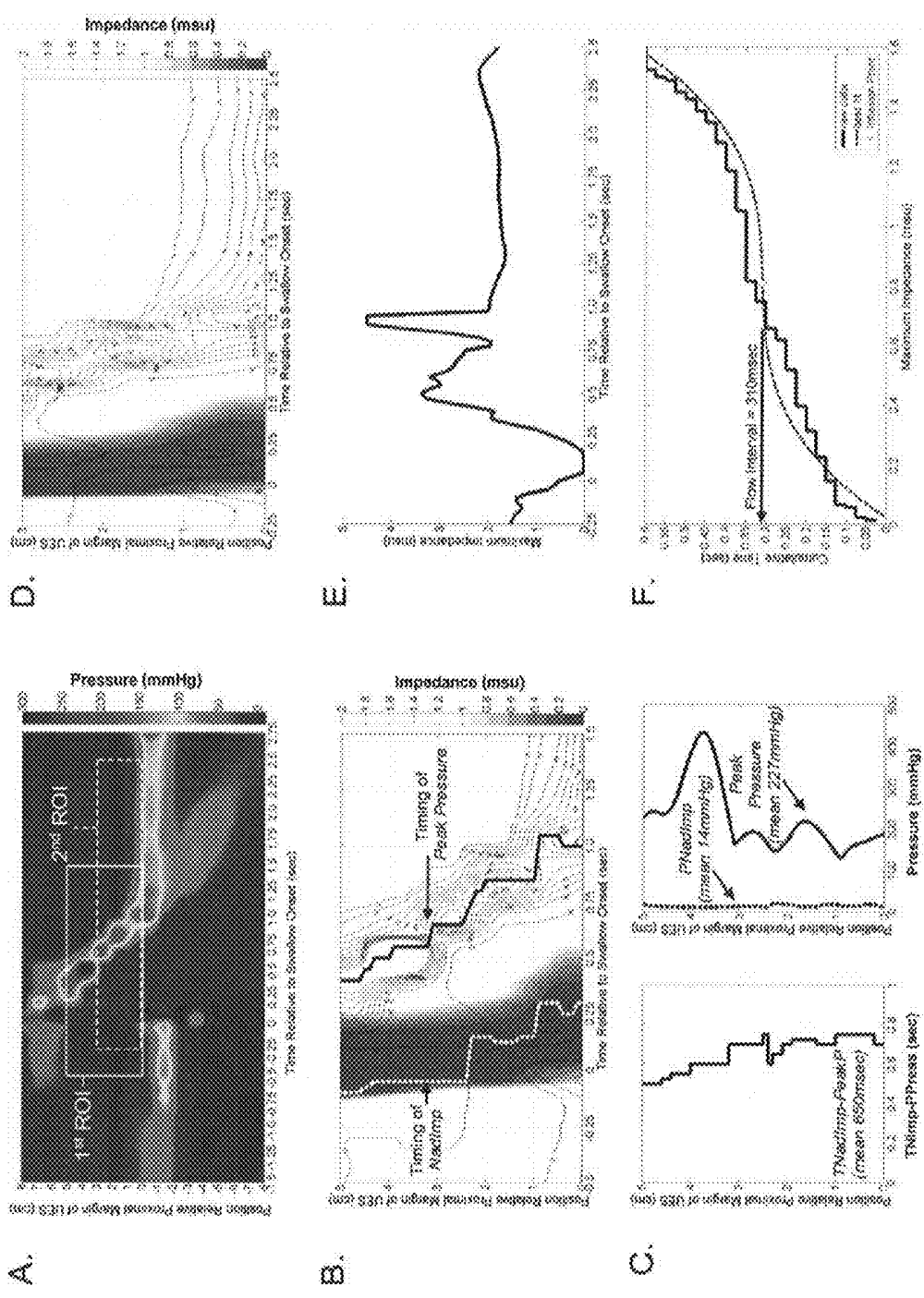


FIGURE 4

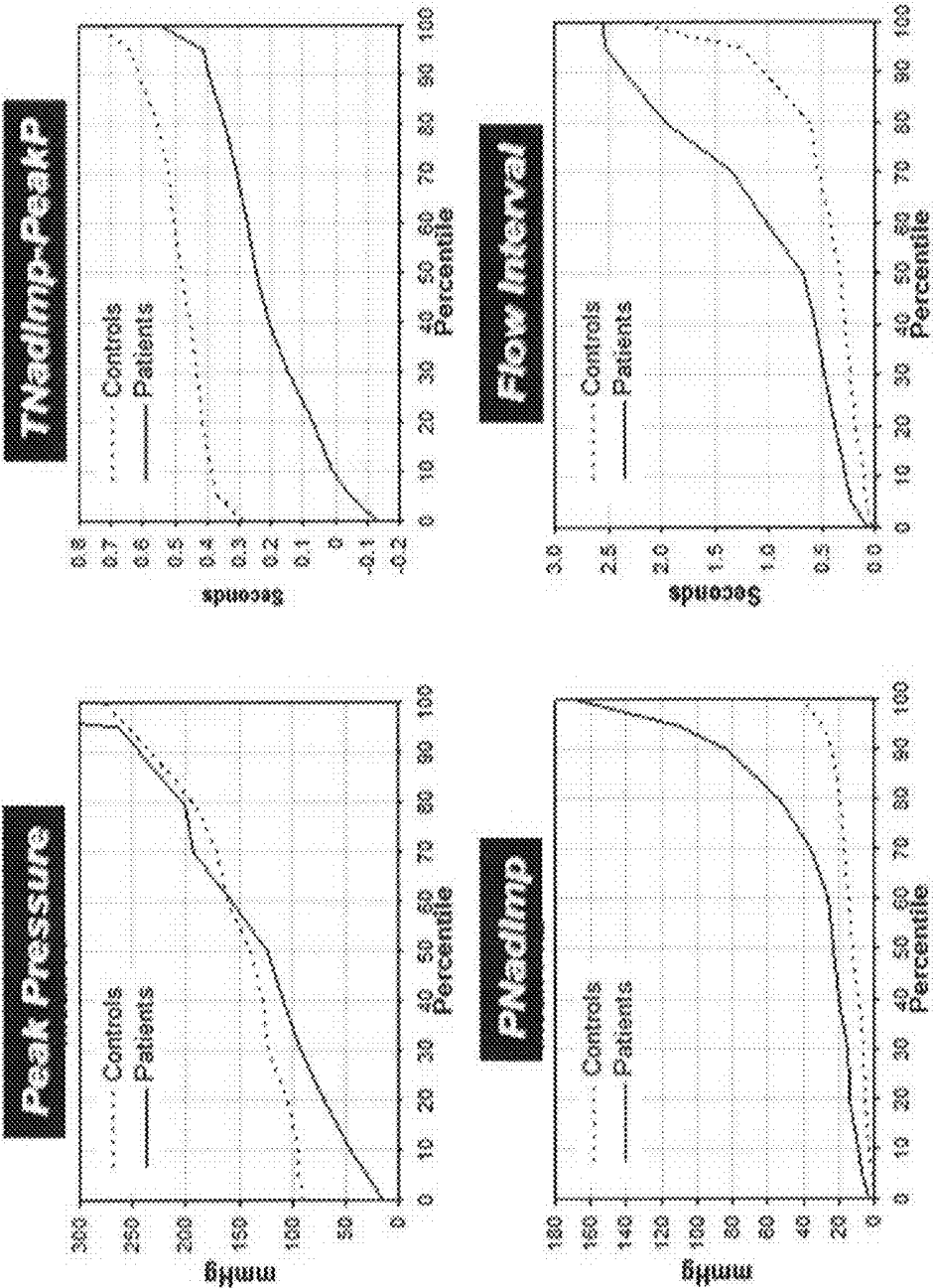


FIGURE 5

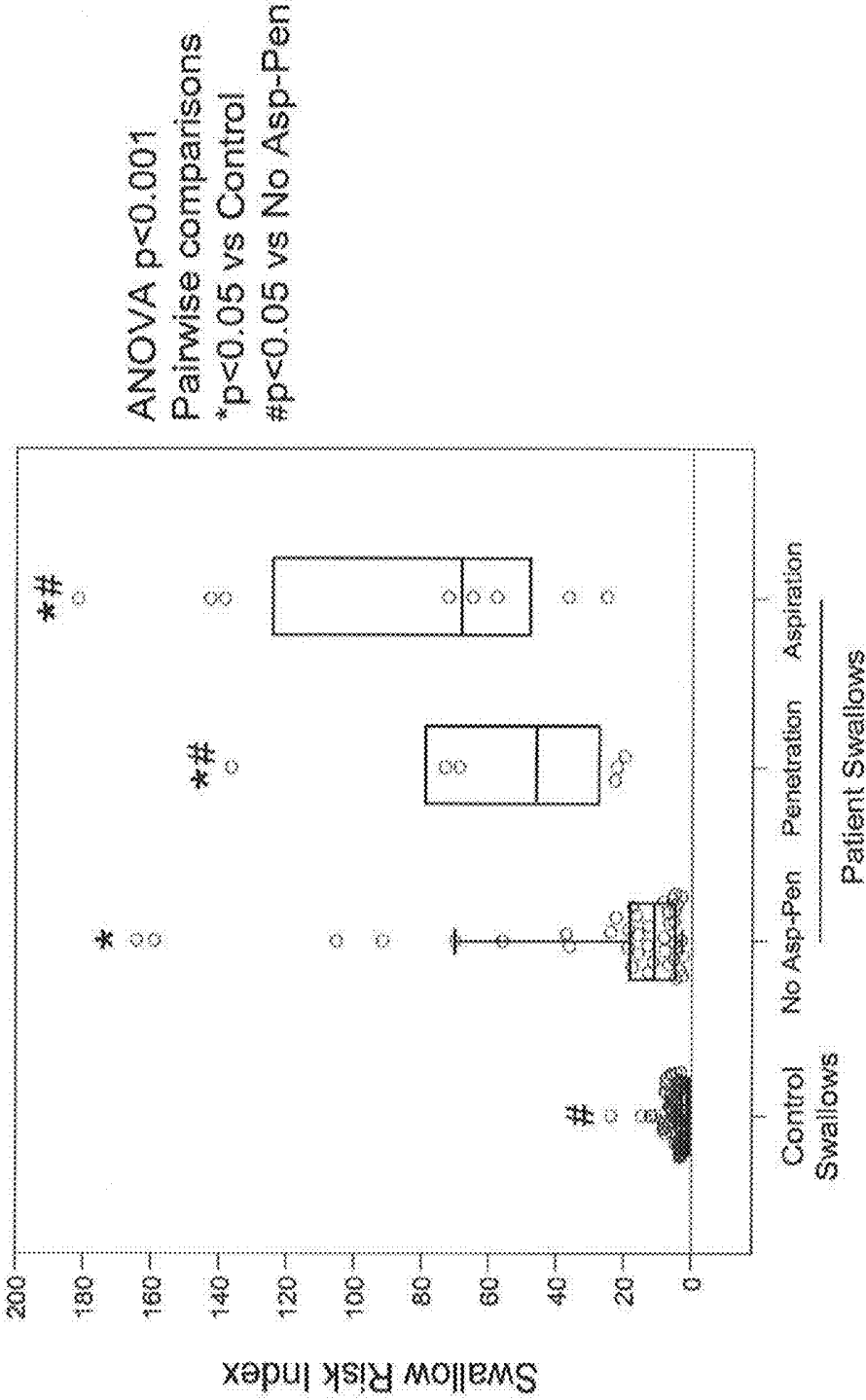


FIGURE 6

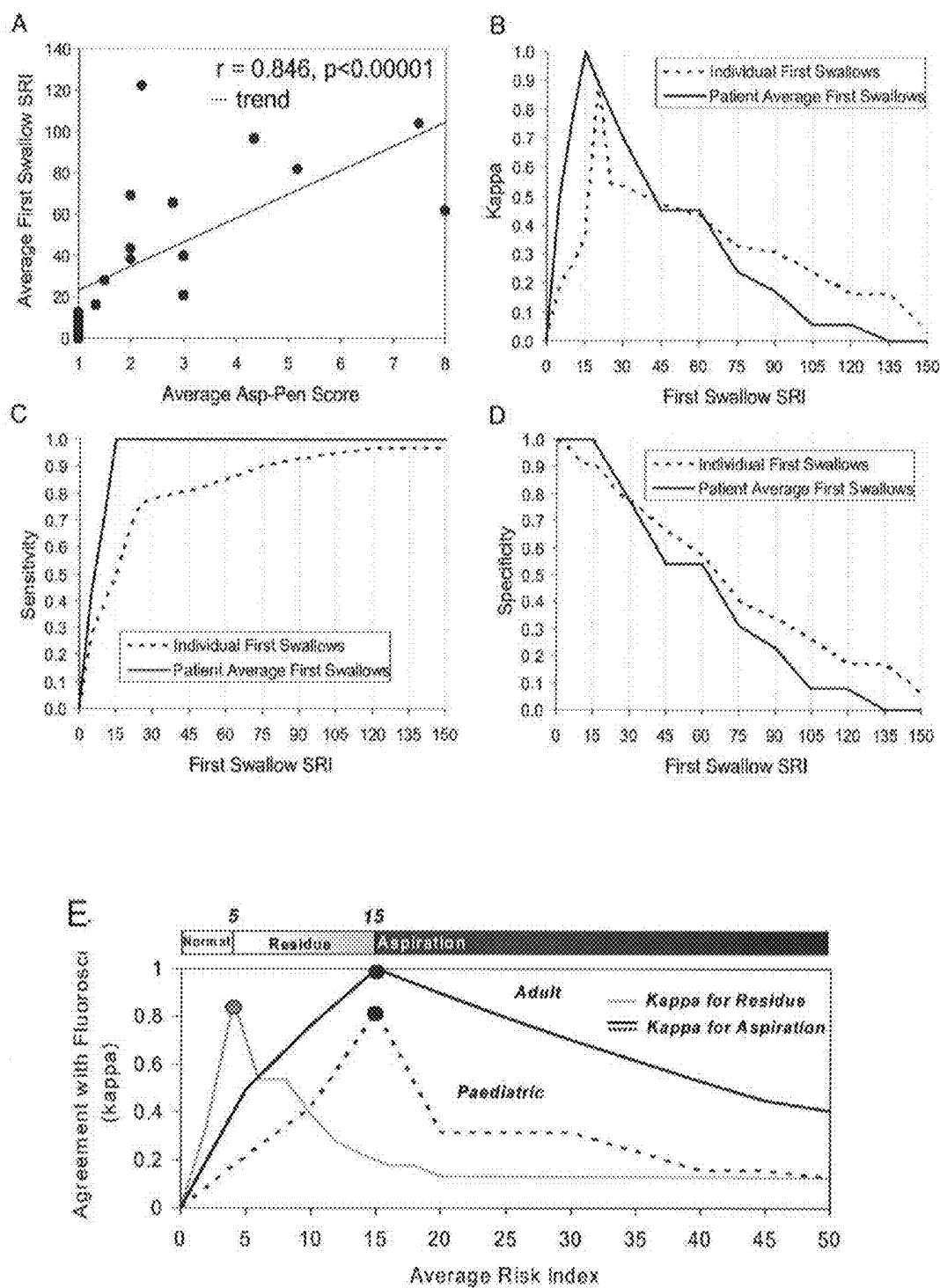


FIGURE 7

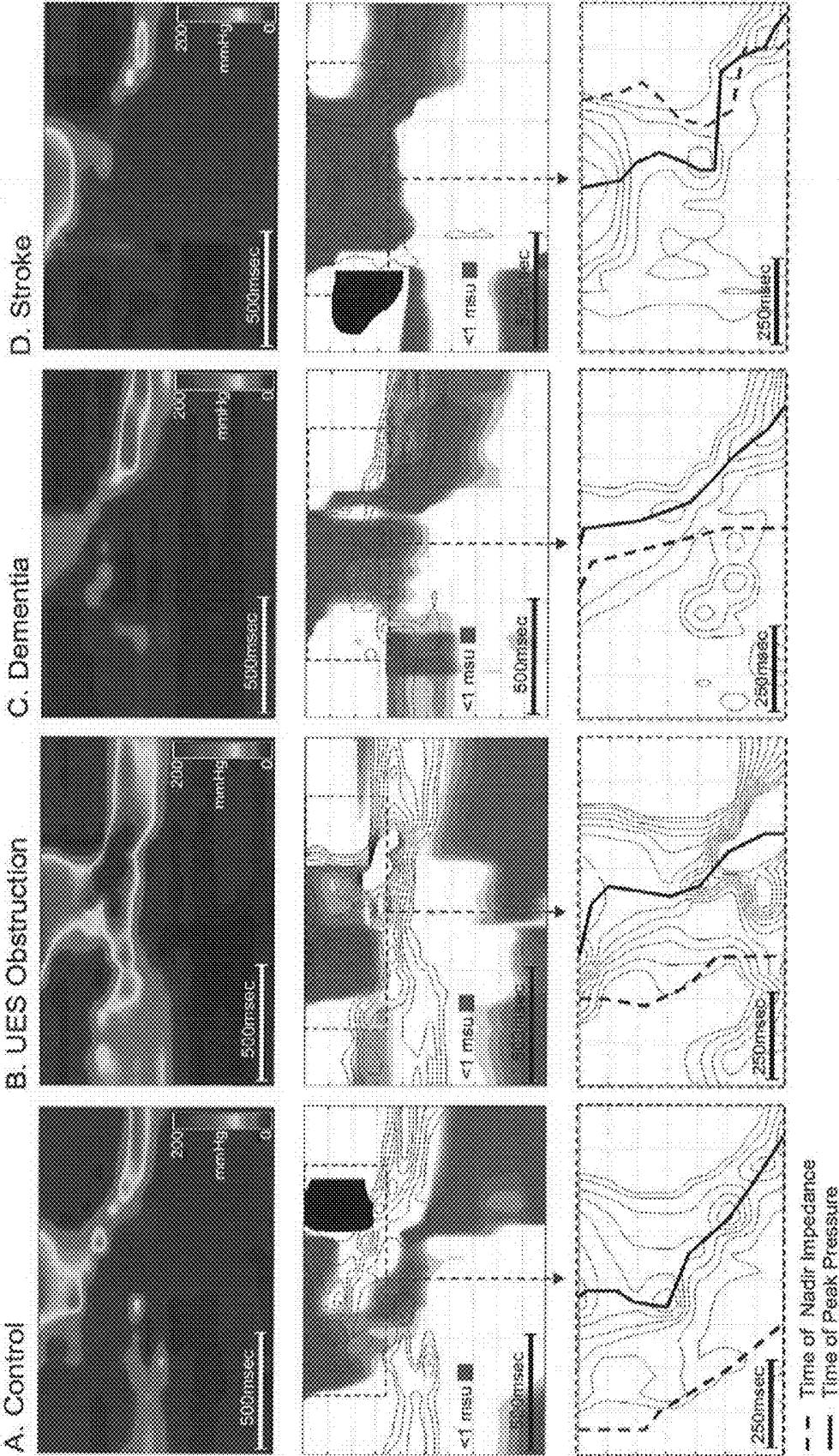


FIGURE 8

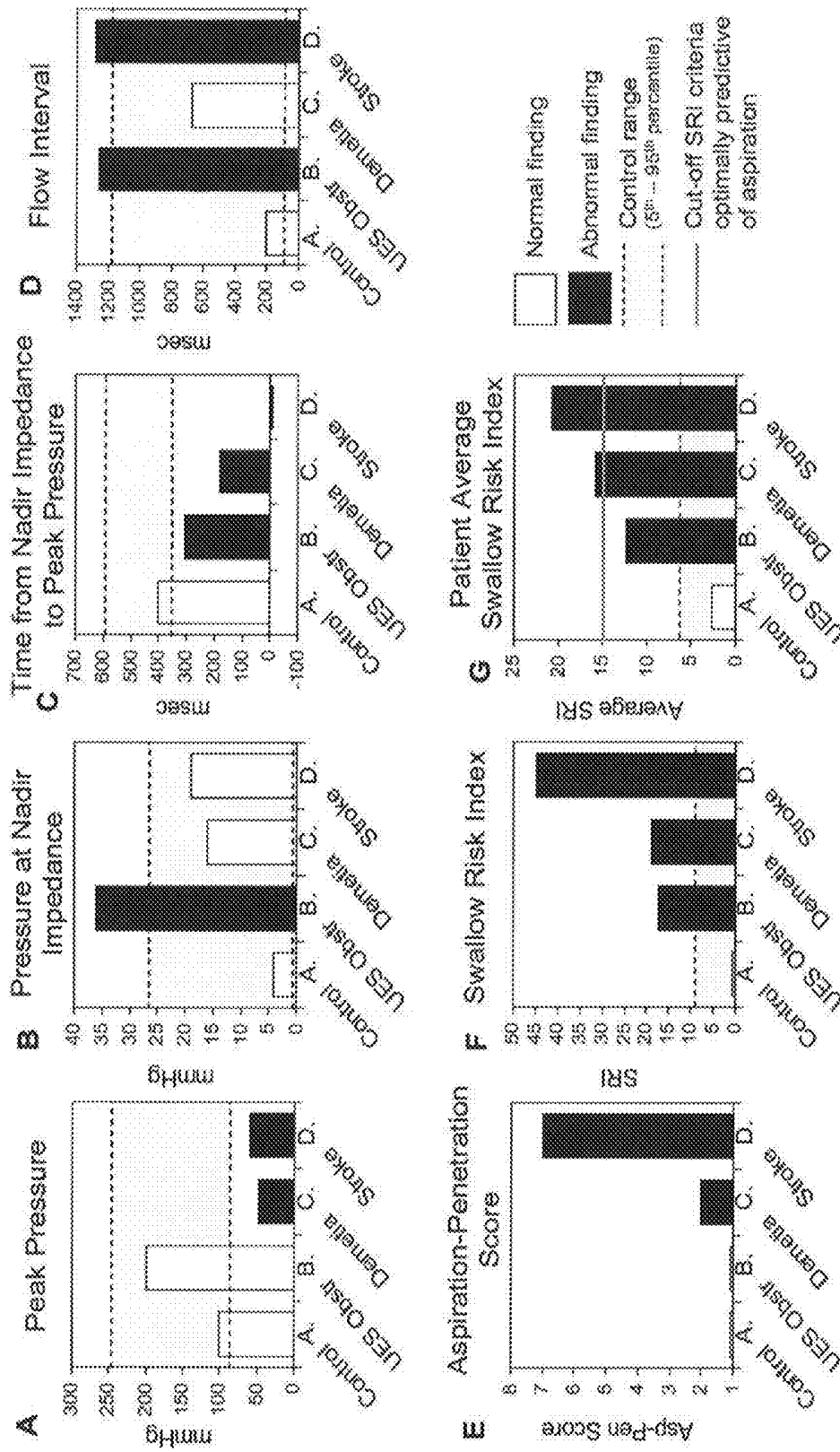


FIGURE 9

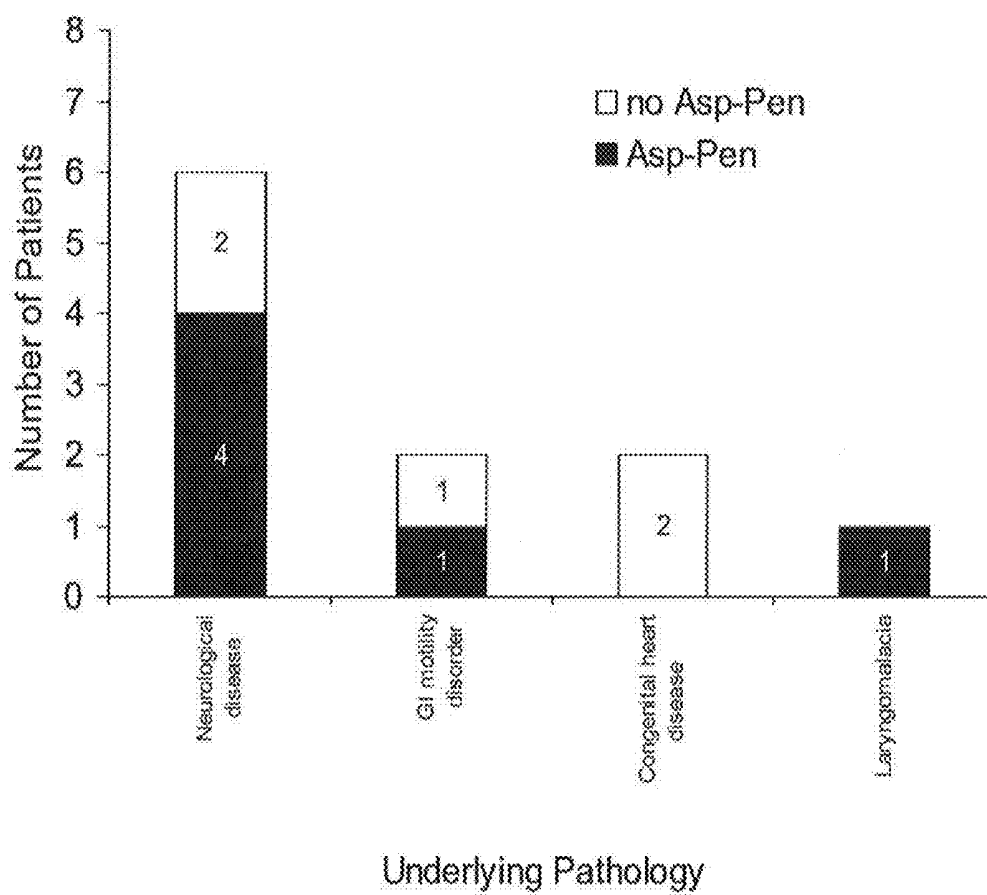


FIGURE 10

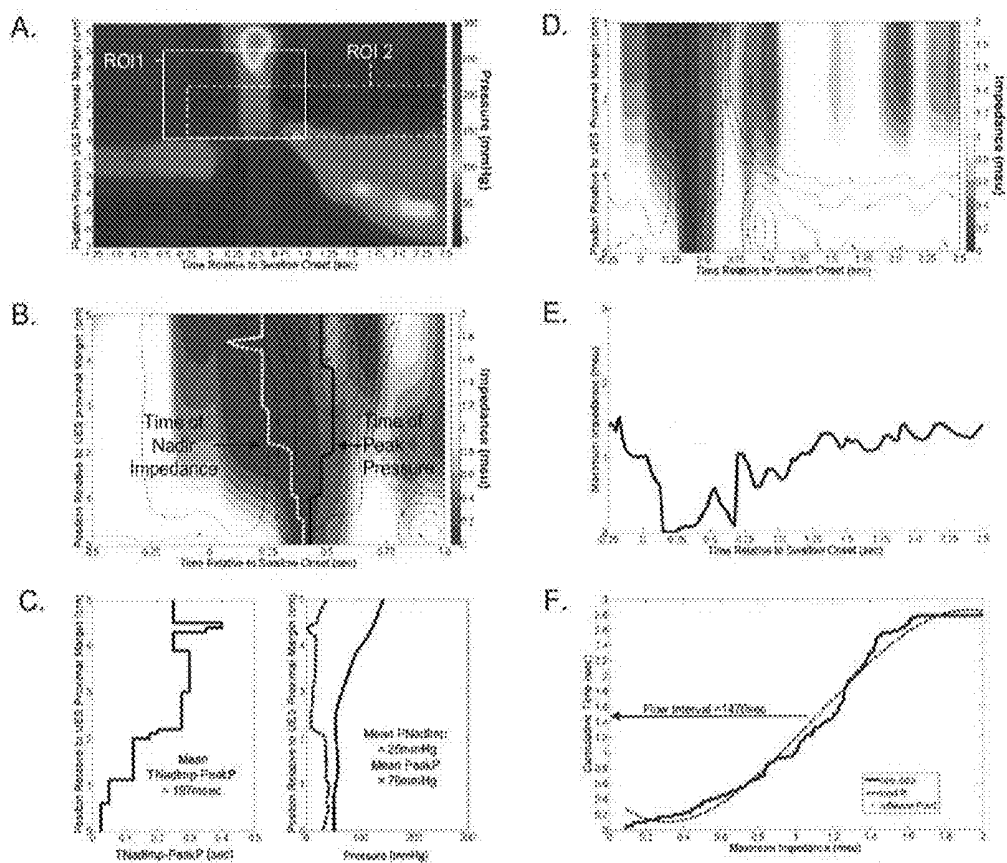


FIGURE 11

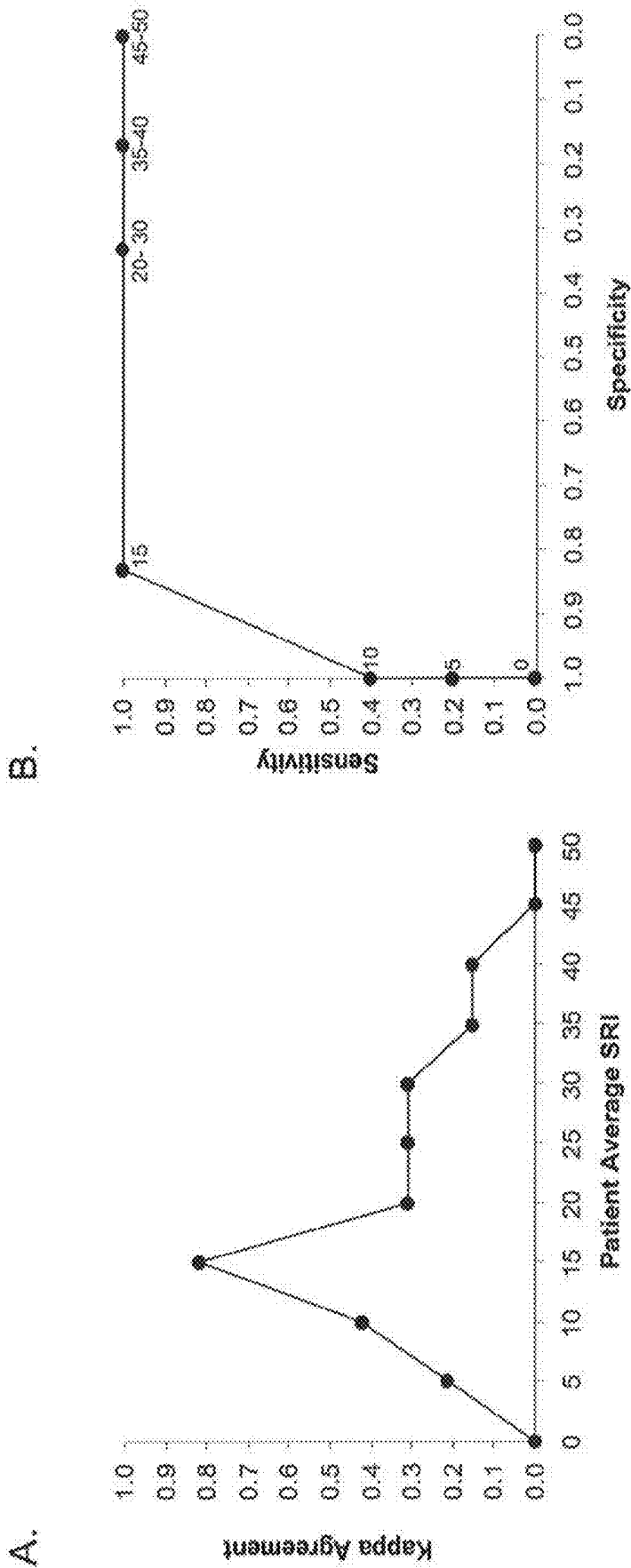


FIGURE 12

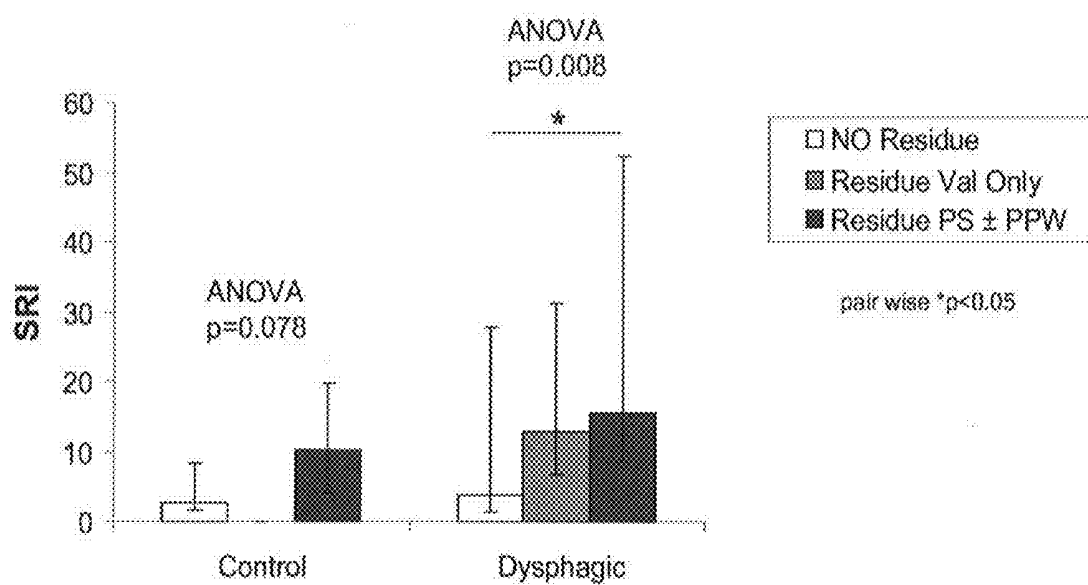


FIGURE 13

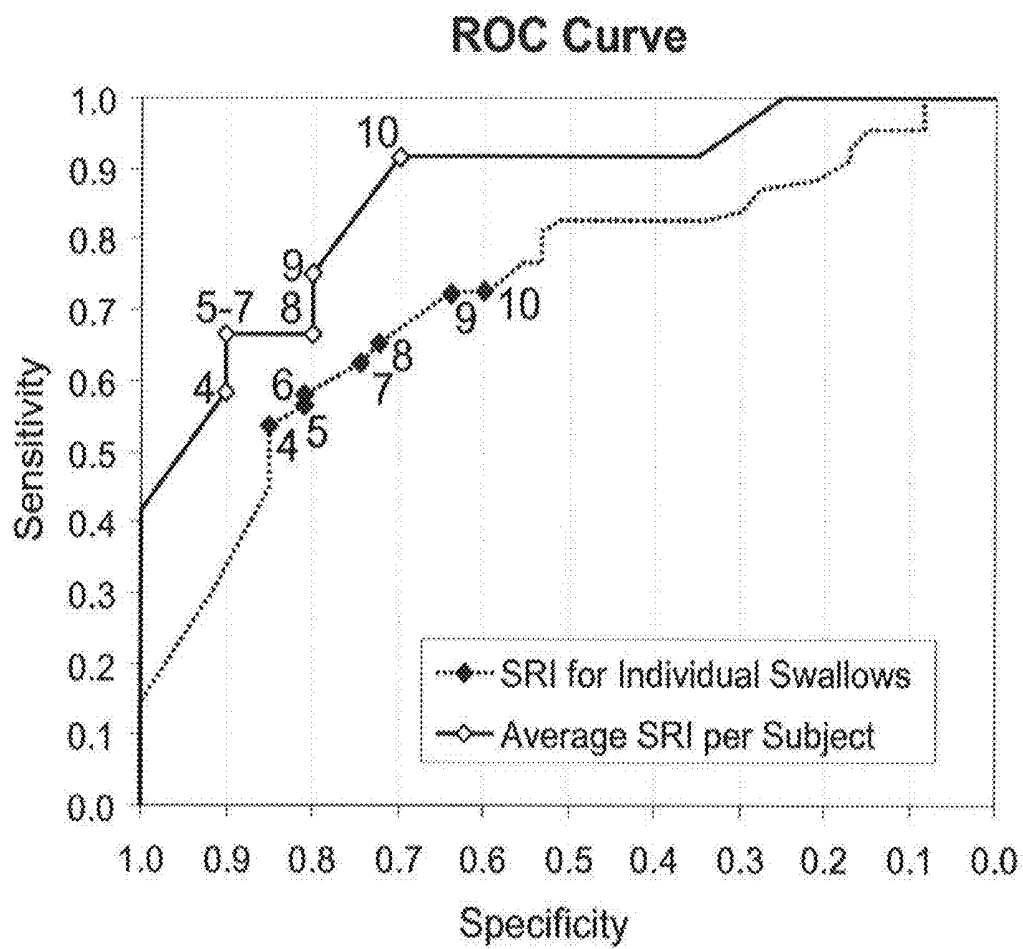


FIGURE 14

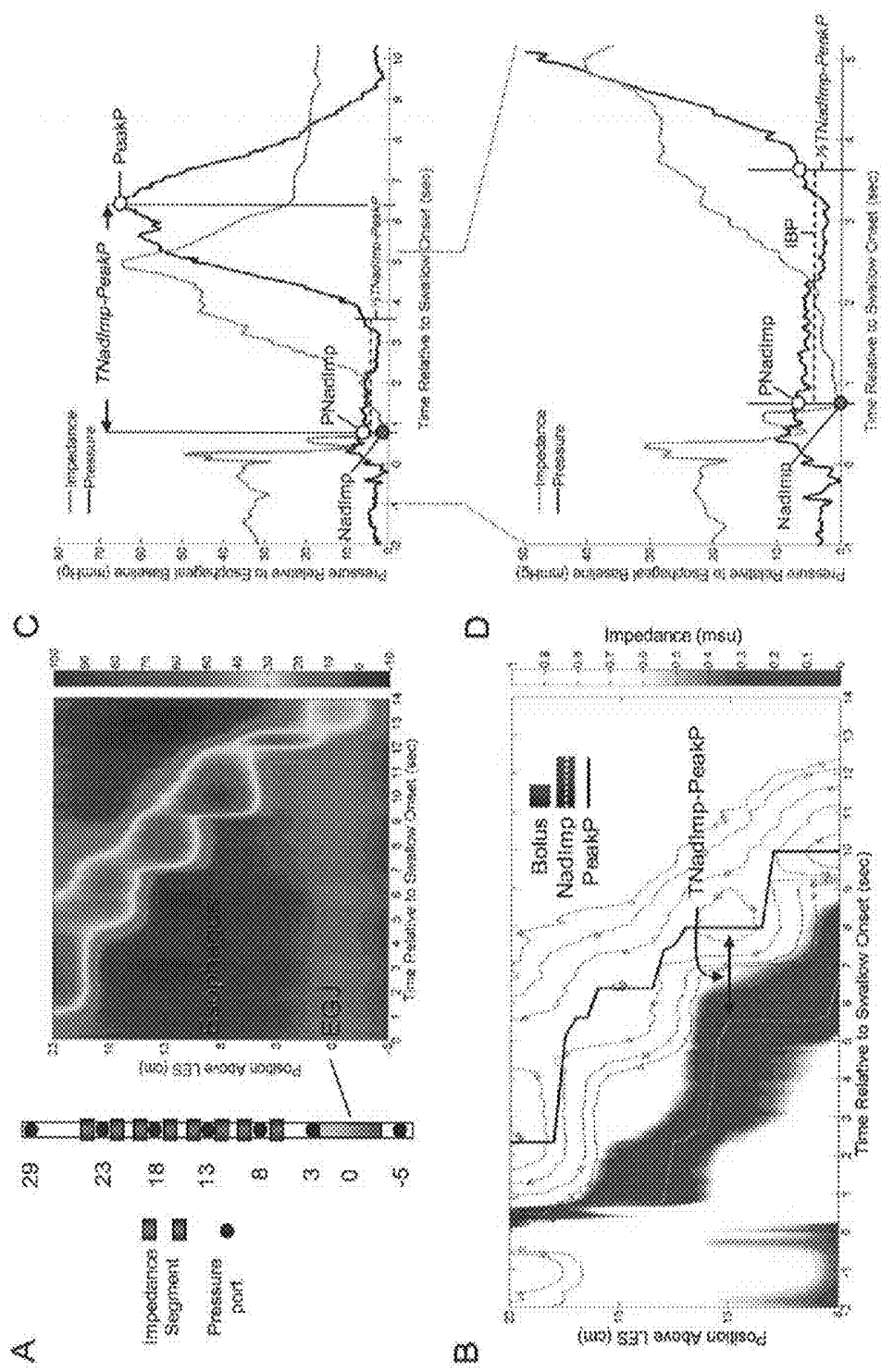


FIGURE 15

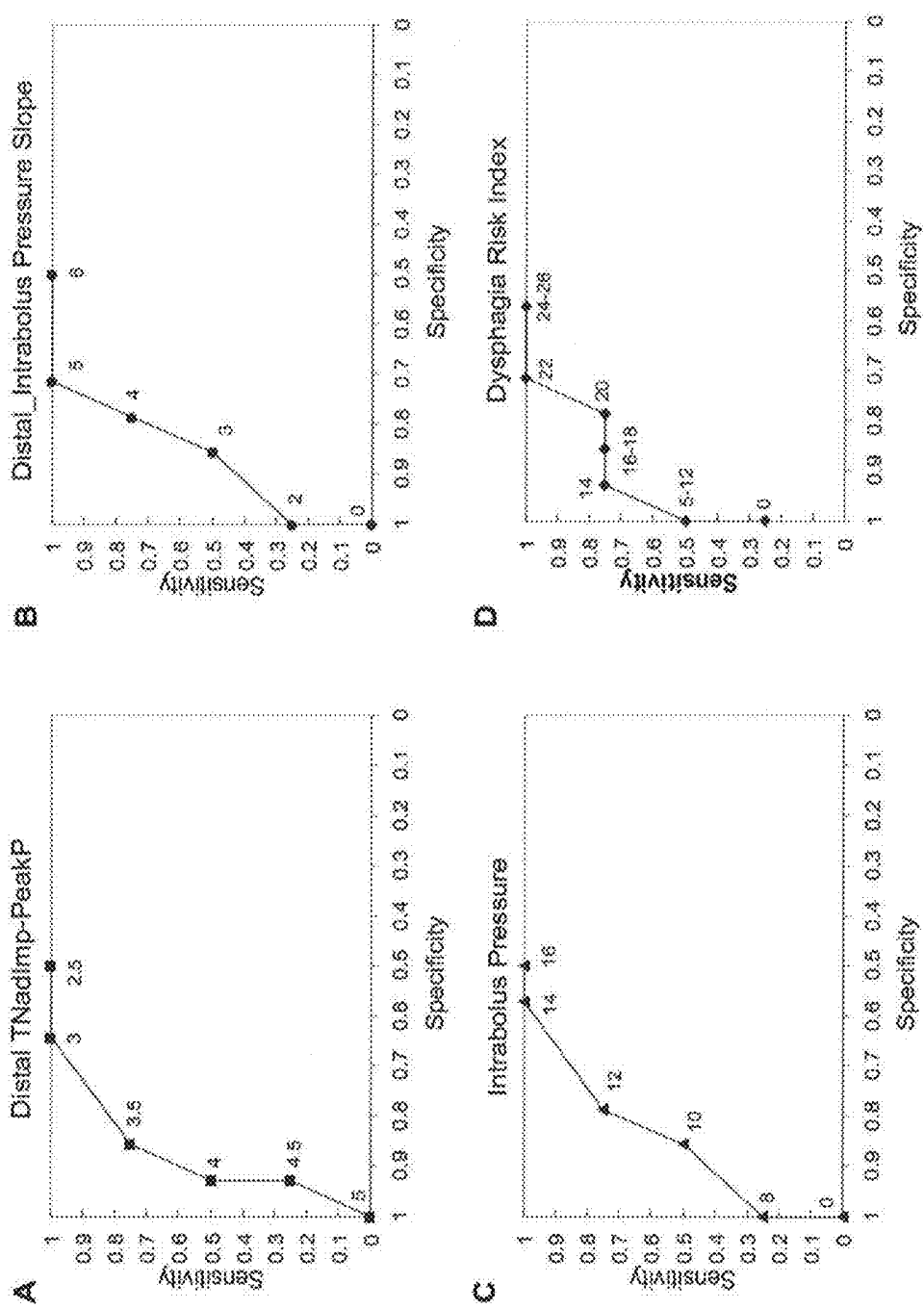


FIGURE 16

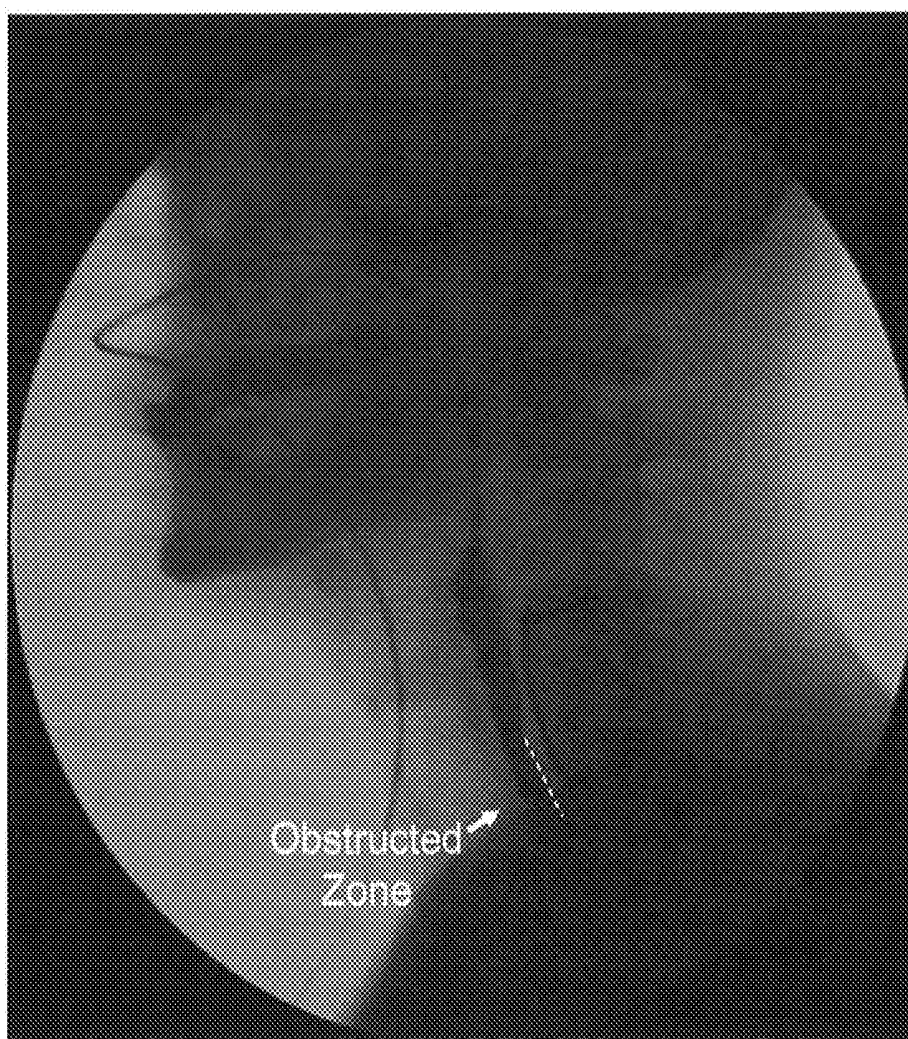


FIGURE 17

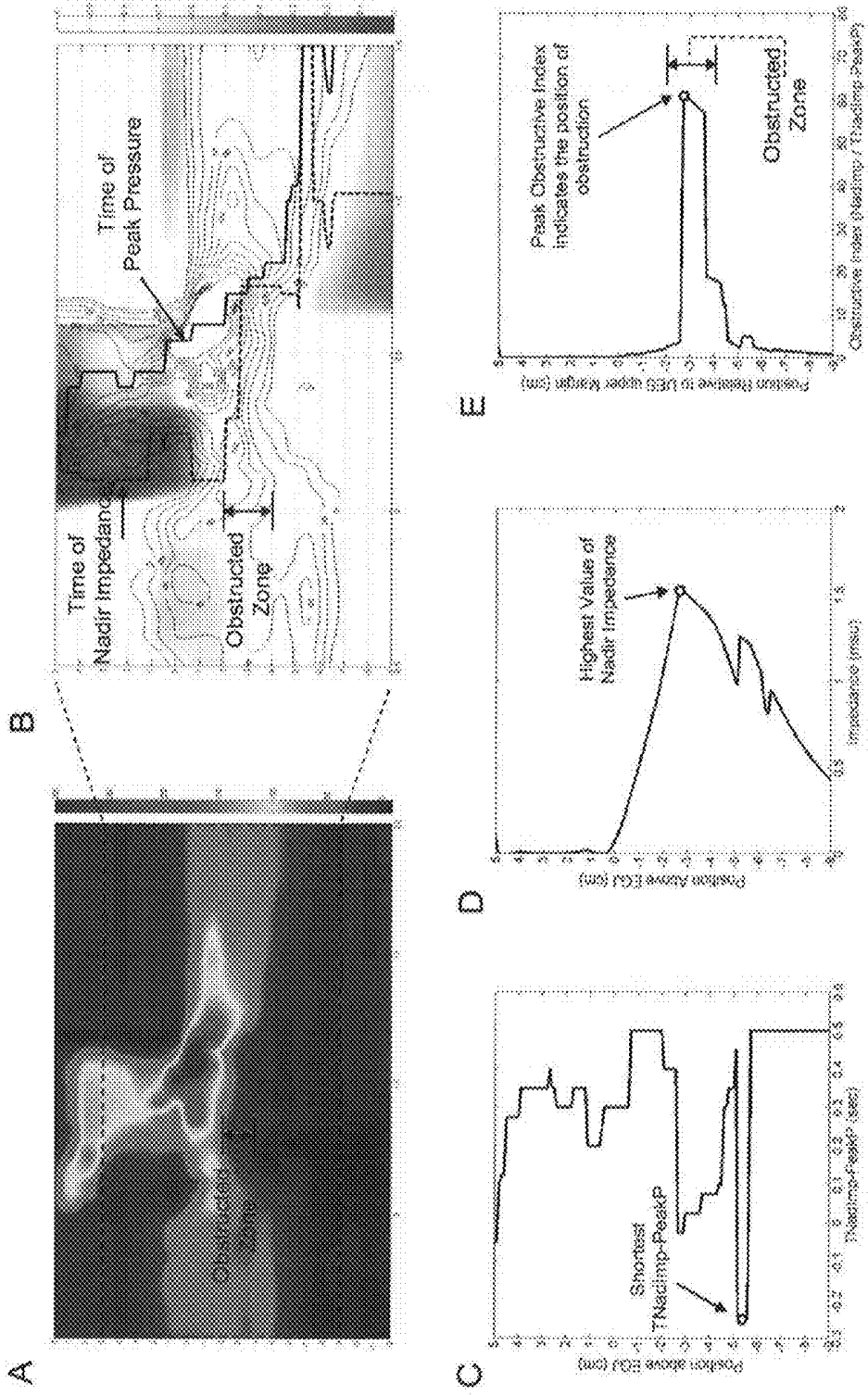


FIGURE 18

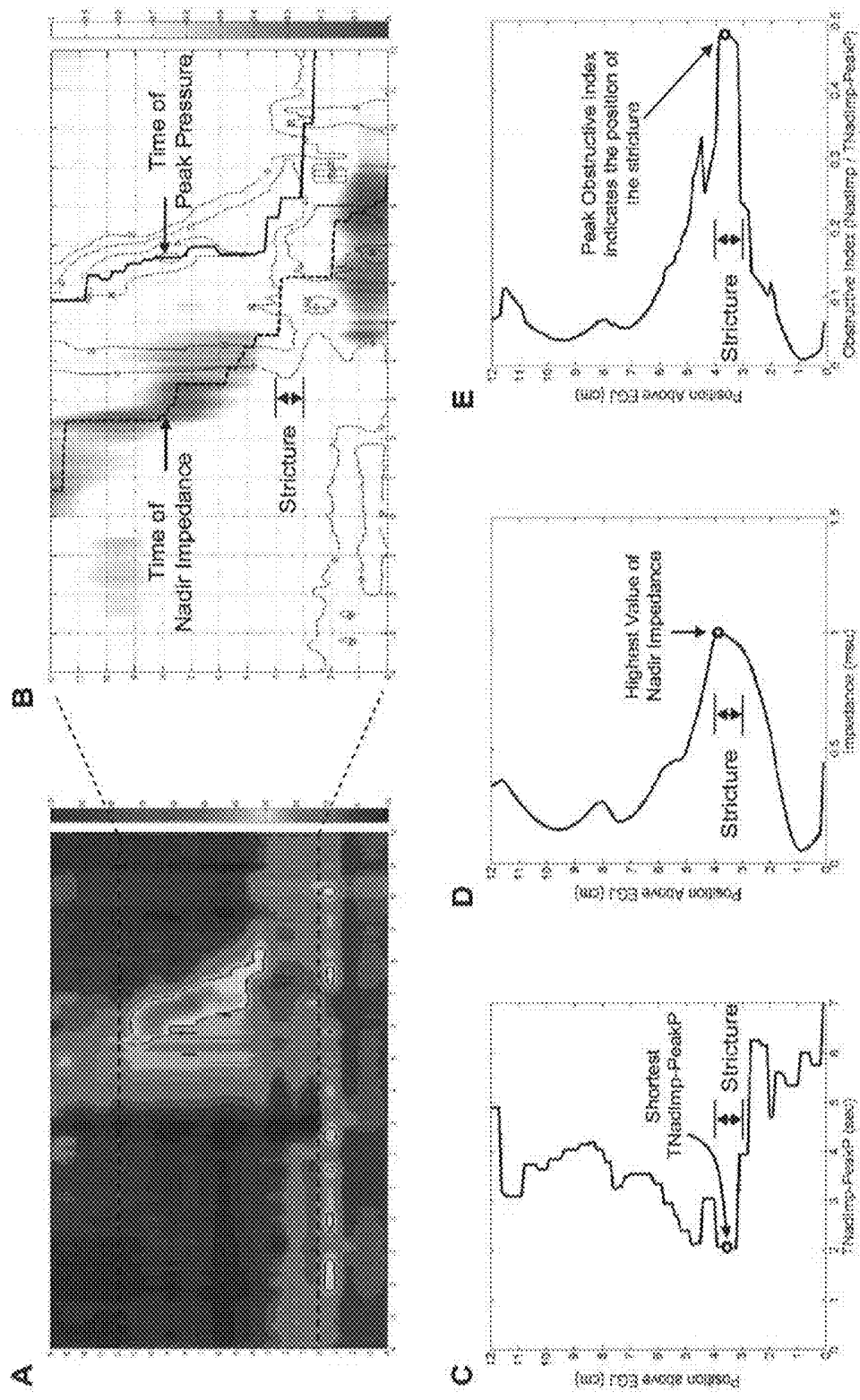


FIGURE 19

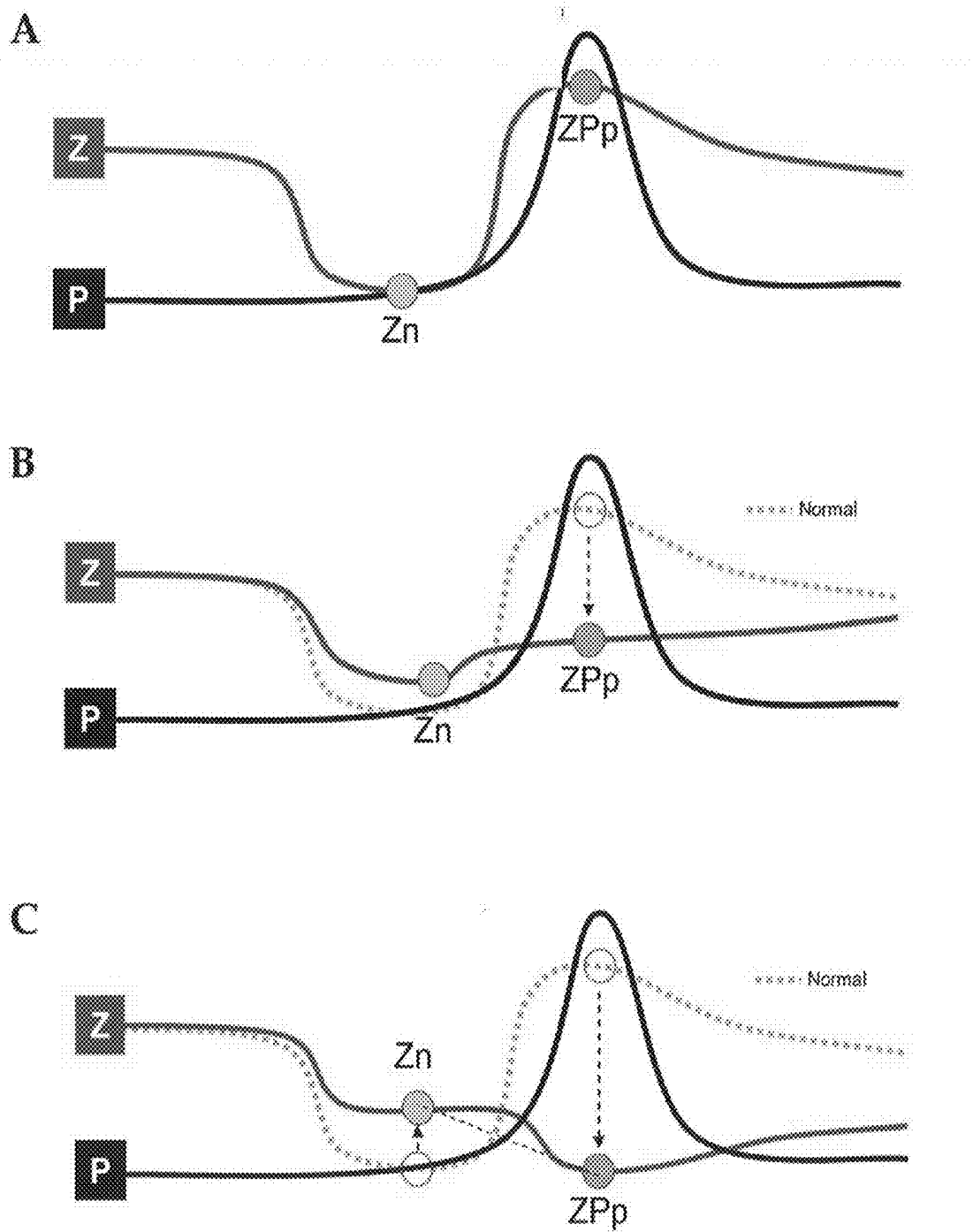


FIGURE 20

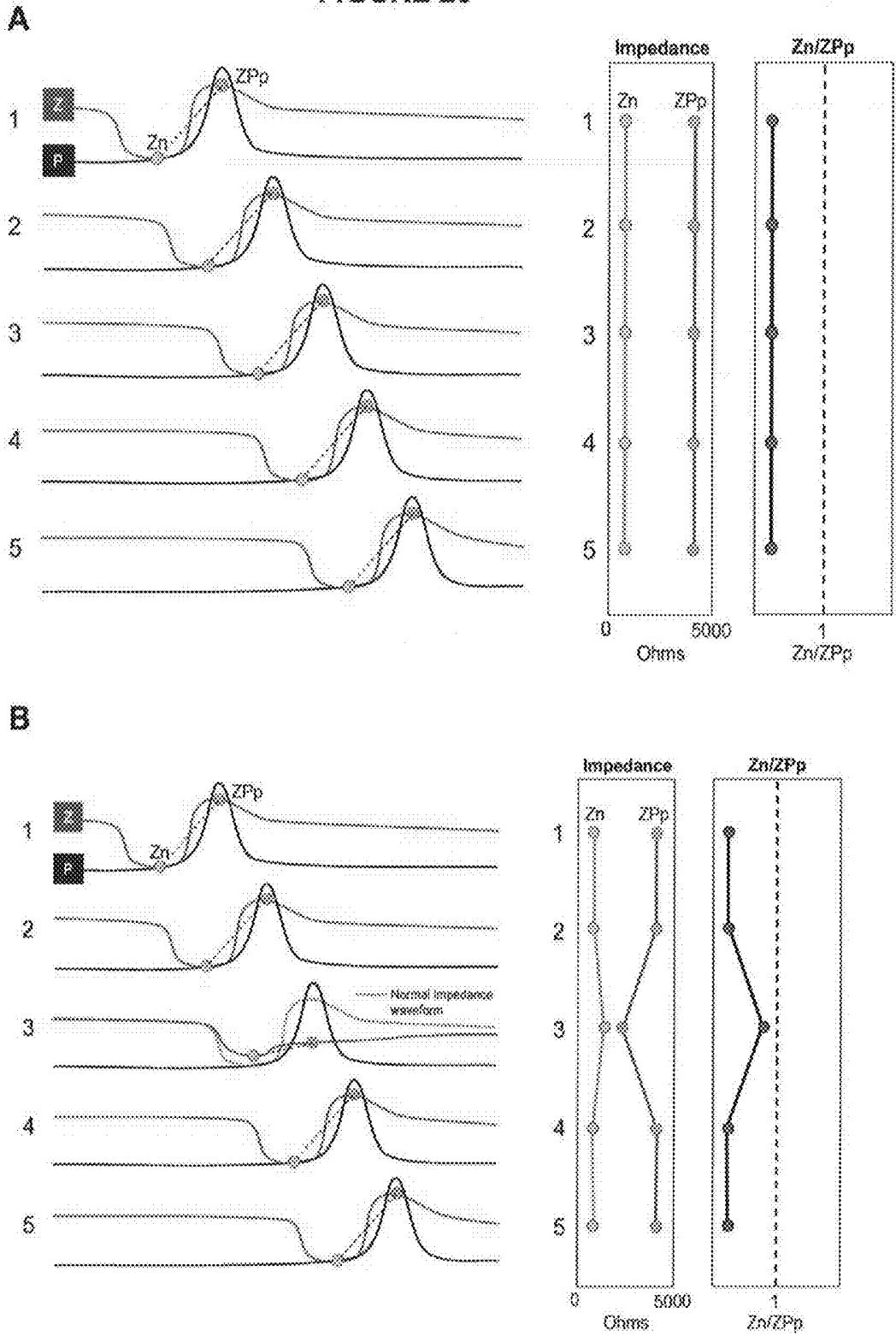


FIGURE 20 (Continued)

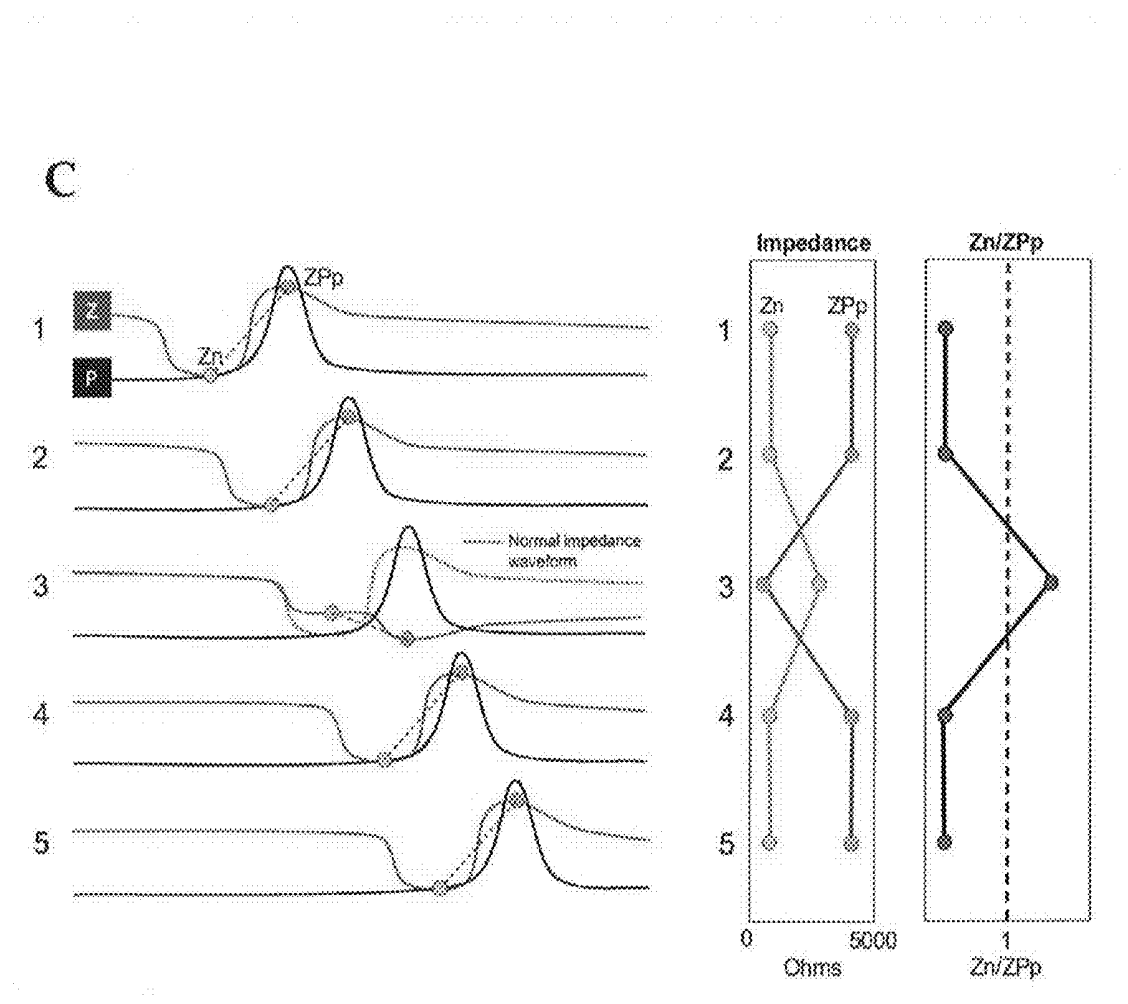


Figure 21

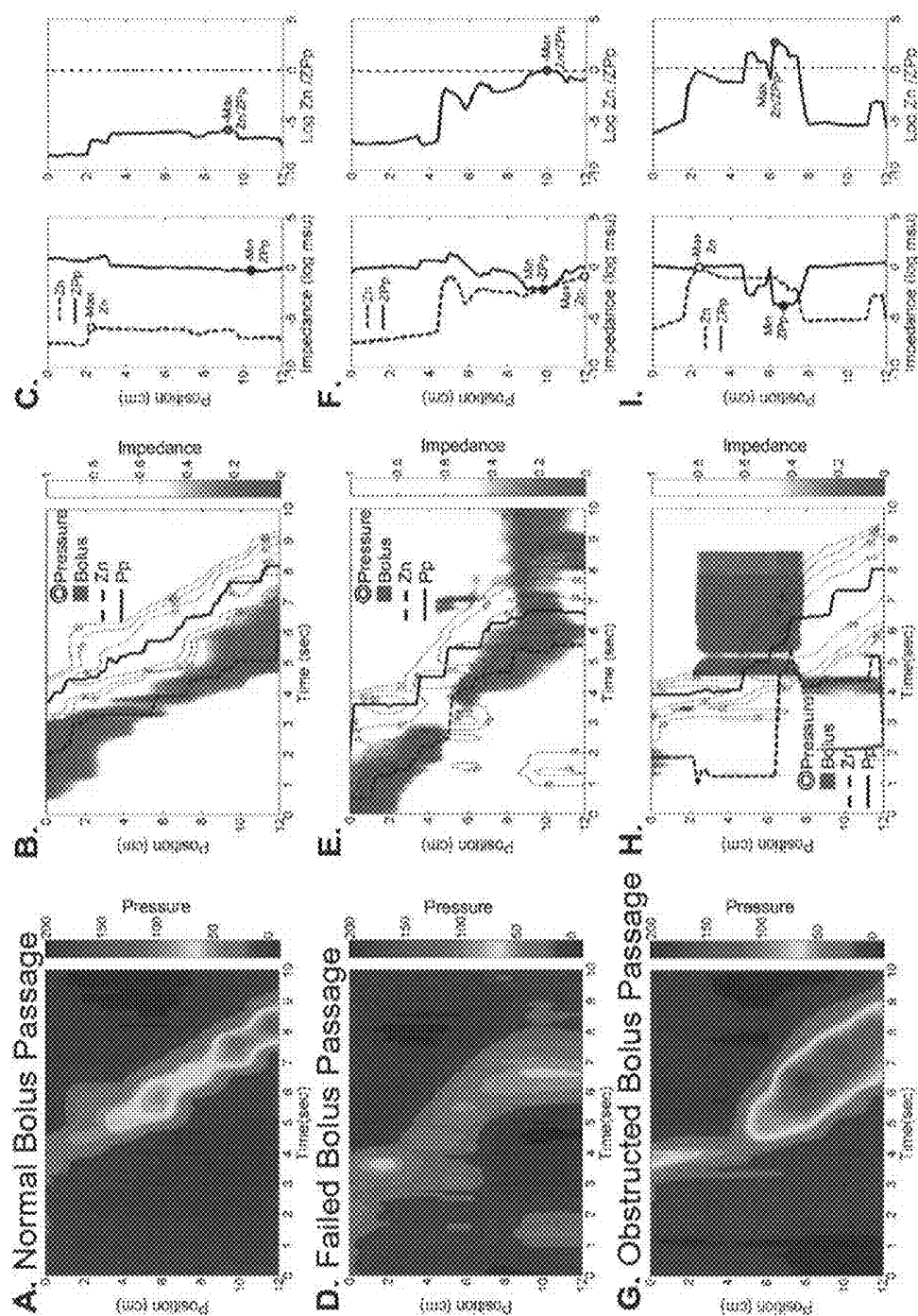


Figure 22

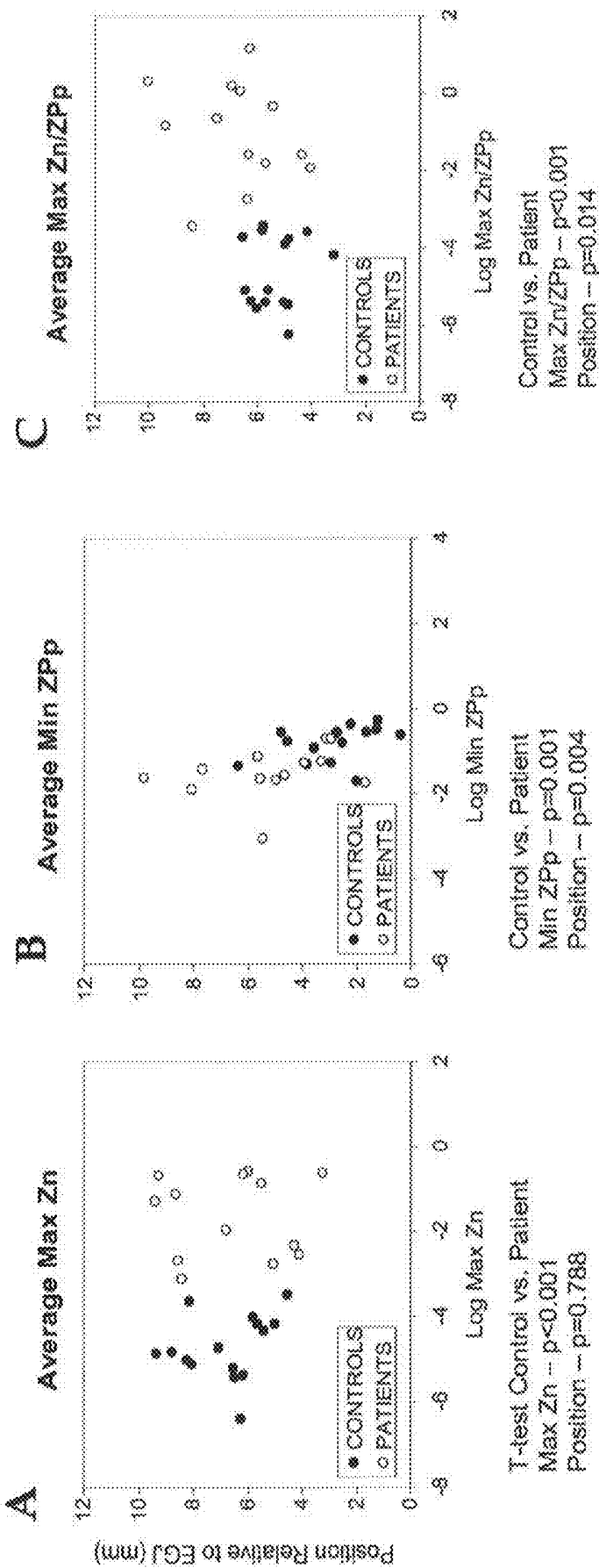


Figure 23

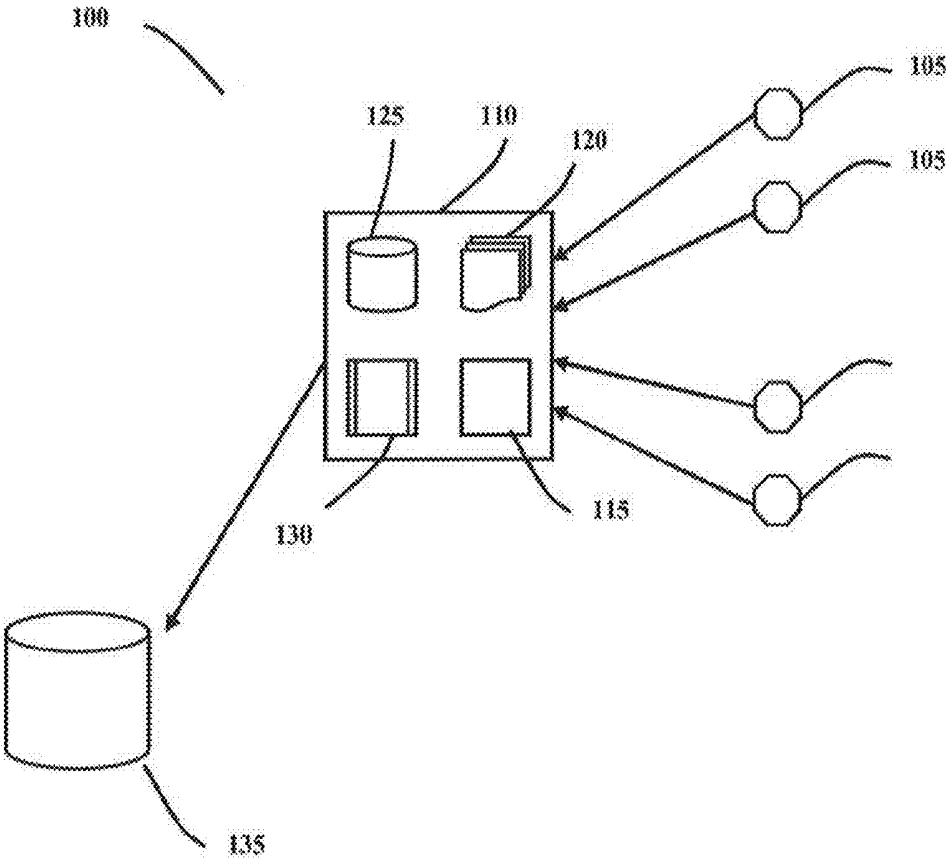


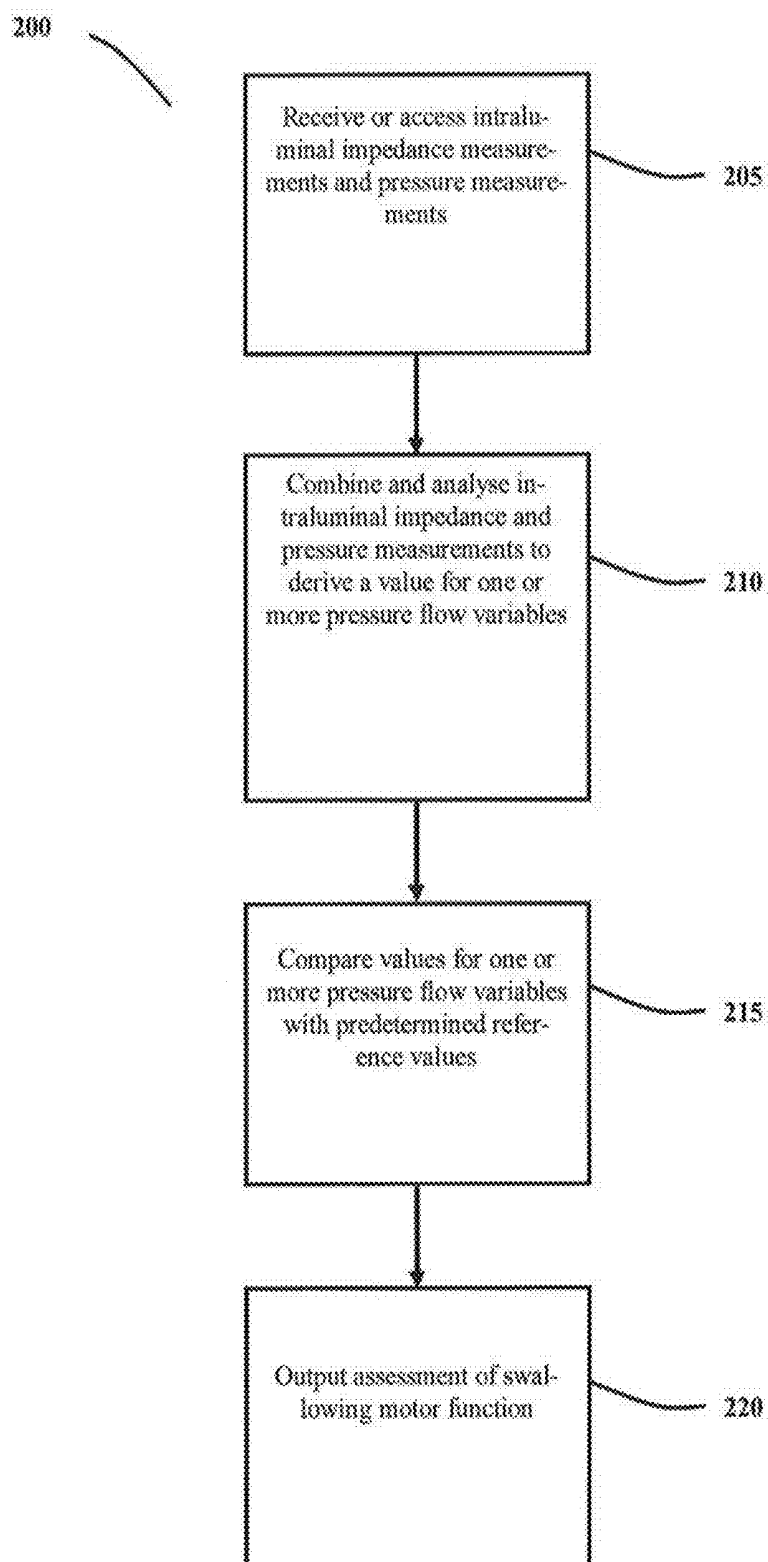
Figure 24

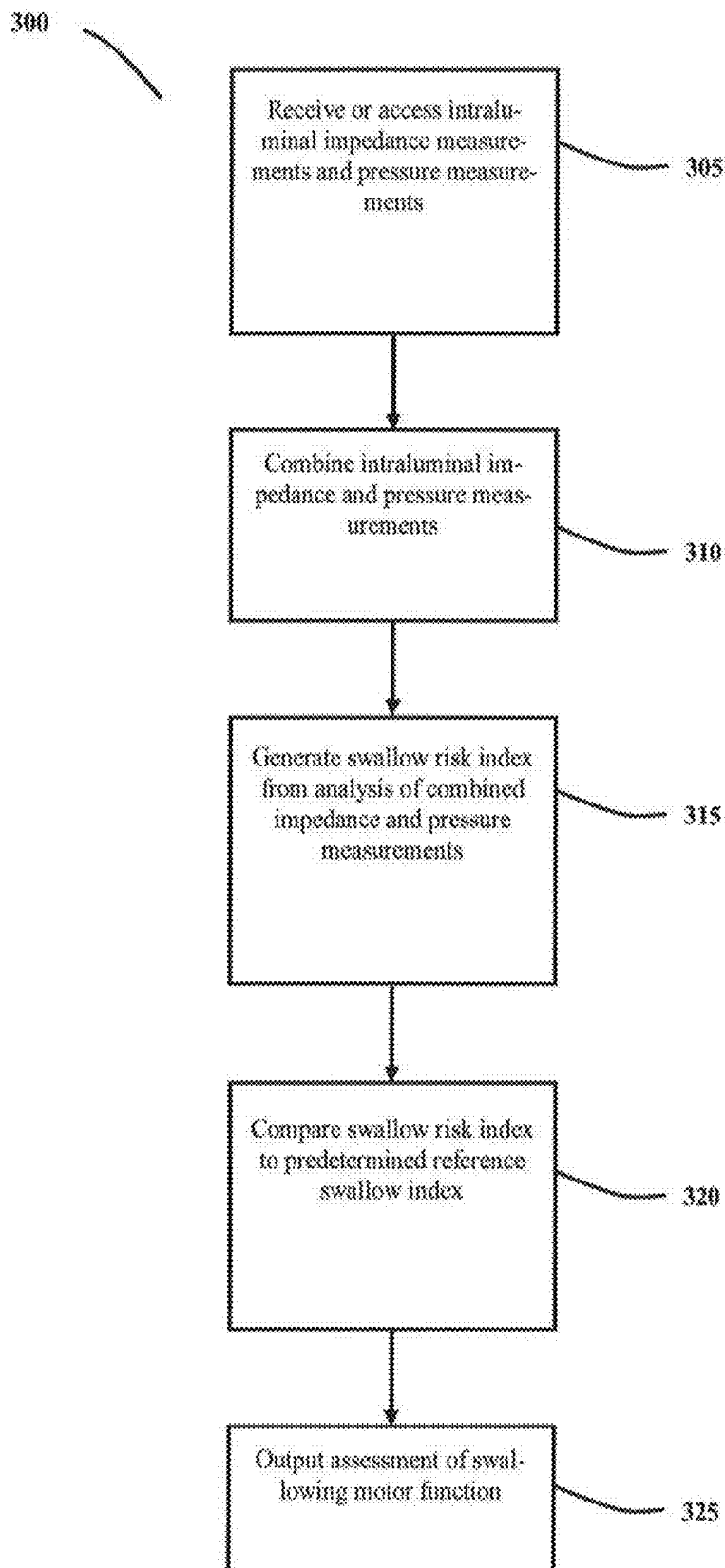
FIGURE 25

FIGURE 26

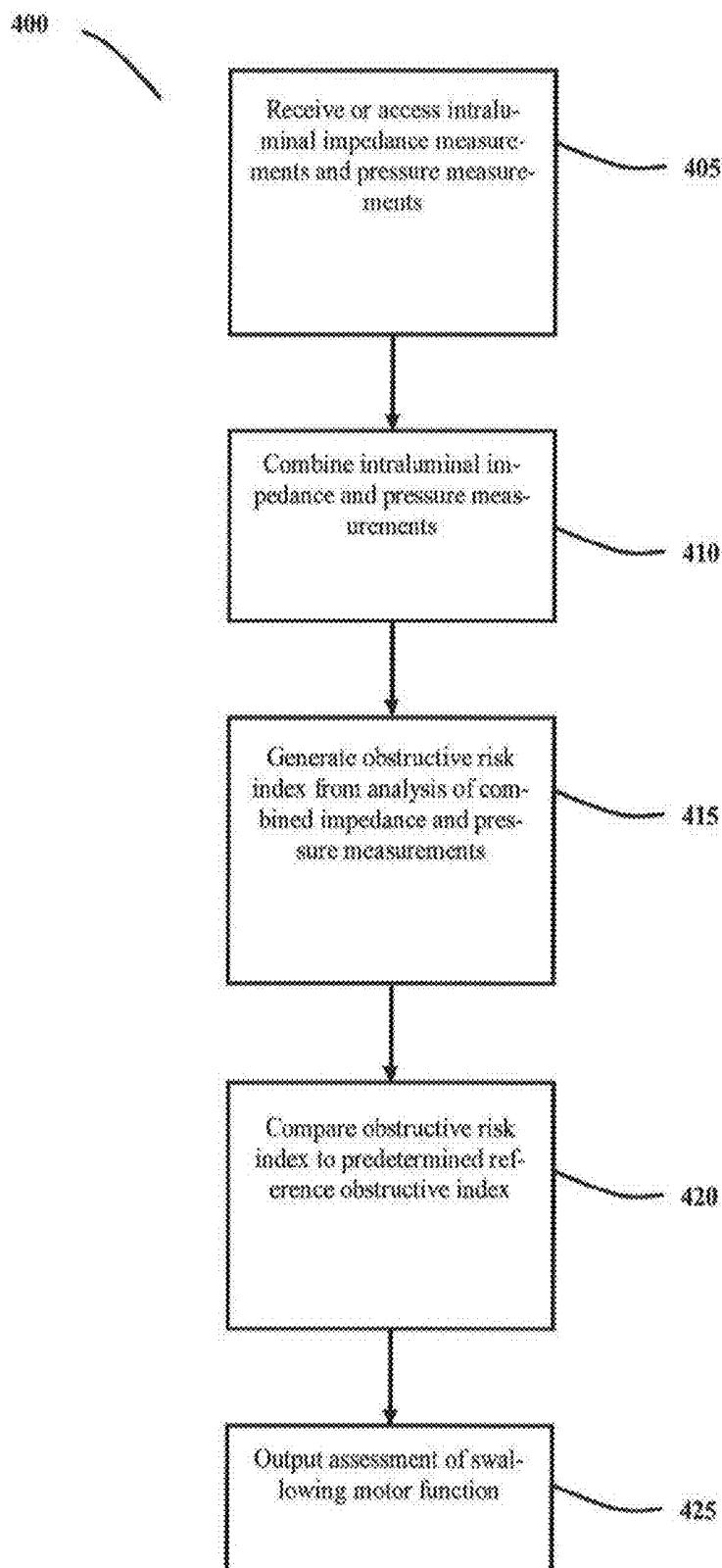


FIGURE 27A

Zdat	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	Zn
Y1	100	100	100	75	50	25	50	75	100	100	100	100	100	100	25.00
Y2	100	100	100	100	75	50	25	50	75	100	100	100	100	100	25.00
Y3	100	100	100	100	100	75	50	25	50	75	100	100	100	100	25.00
Y4	100	100	100	100	100	100	75	50	25	50	75	100	100	100	25.00
Y5	100	100	100	100	100	100	100	75	50	25	50	75	100	100	25.00

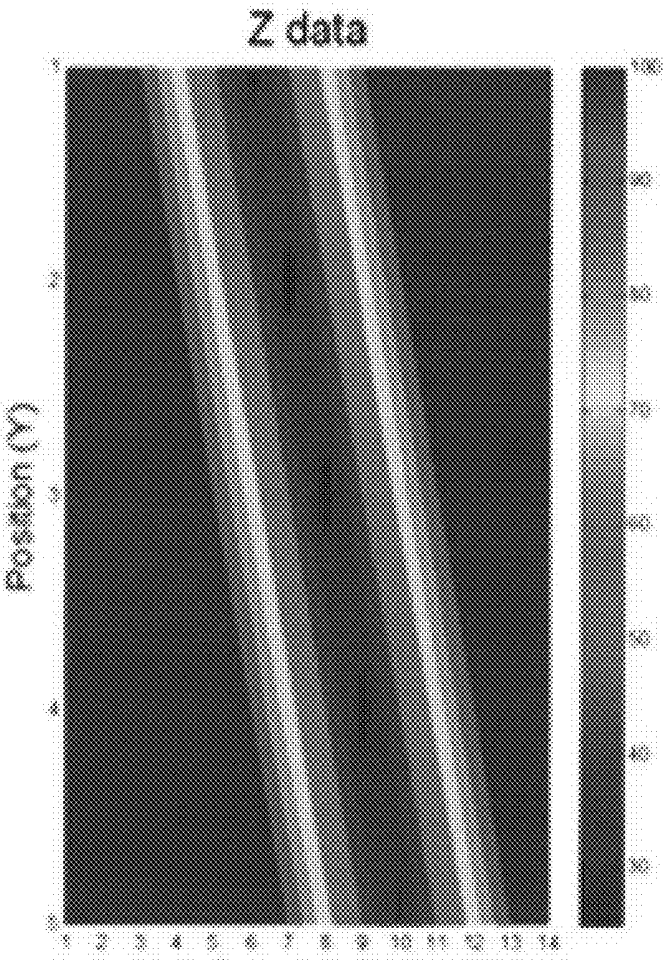


FIGURE 27B

Zn	Zn/Z	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14
25.00	Y1	0.25	0.25	0.25	0.33	0.50	1.00	0.50	0.33	0.25	0.25	0.25	0.25	0.25	0.25
25.00	Y2	0.25	0.25	0.25	0.25	0.33	0.50	1.00	0.50	0.33	0.25	0.25	0.25	0.25	0.25
25.00	Y3	0.25	0.25	0.25	0.25	0.25	0.33	0.50	1.00	0.50	0.33	0.25	0.25	0.25	0.25
25.00	Y4	0.25	0.25	0.25	0.25	0.25	0.25	0.33	0.50	1.00	0.50	0.33	0.25	0.25	0.25
25.00	Y5	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.33	0.50	1.00	0.50	0.33	0.25	0.25

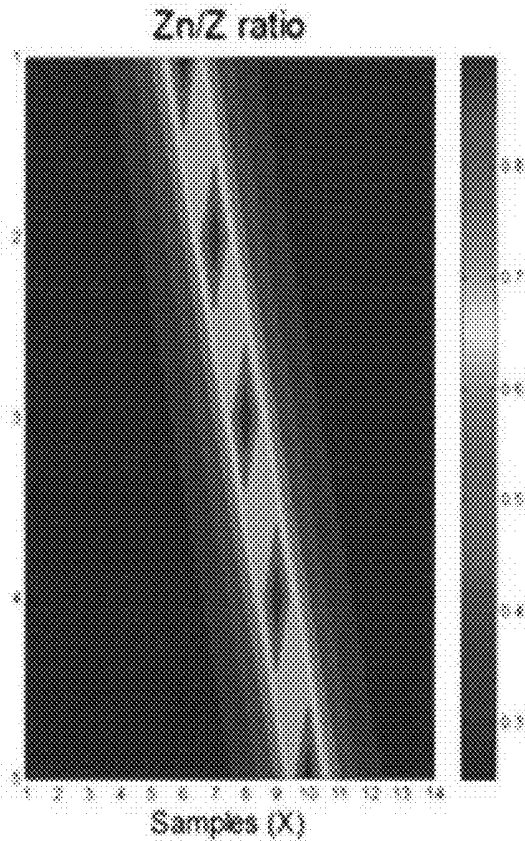


FIGURE 28

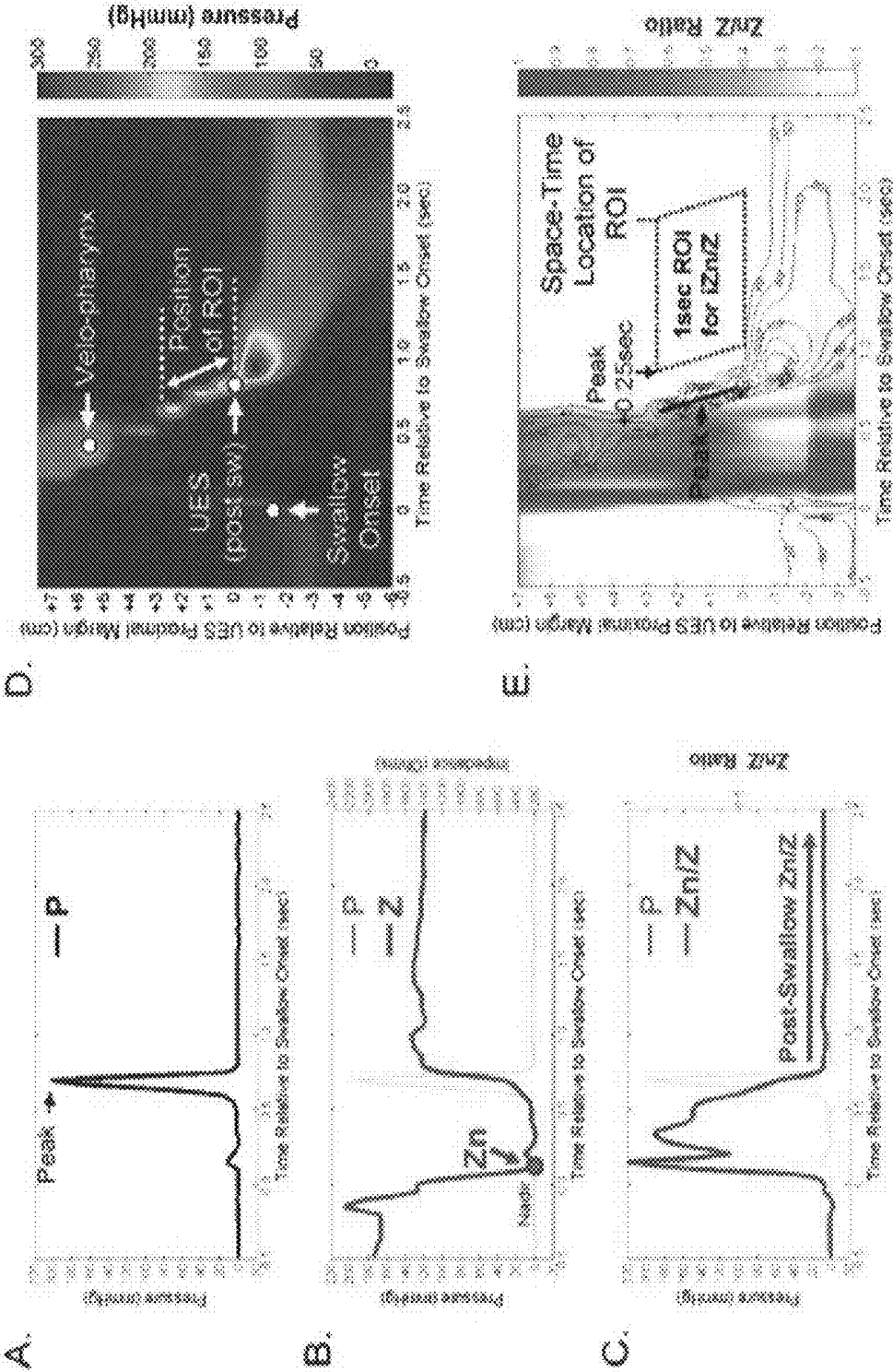
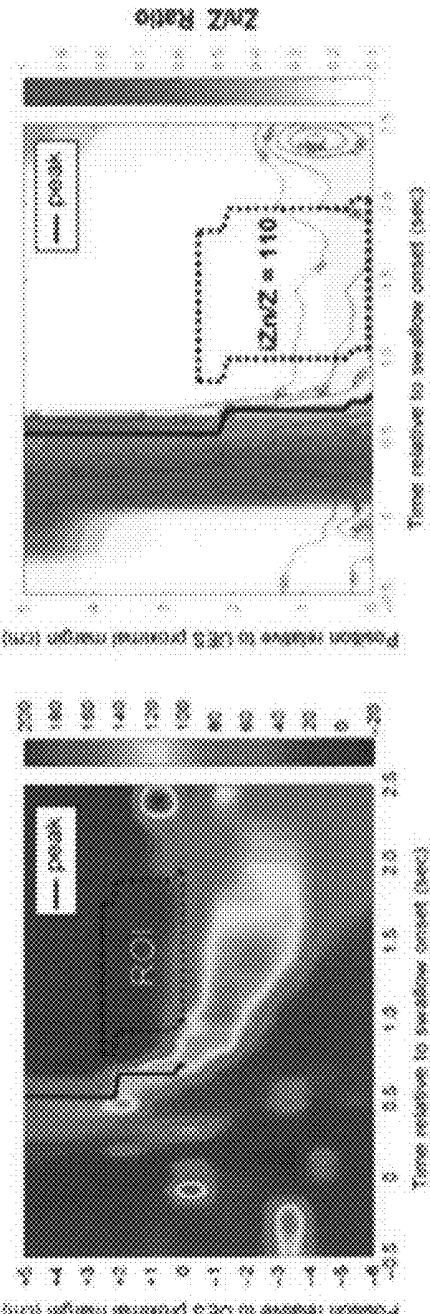


FIGURE 29

10 mL semisolid swallow without bolus residue (Consensus BRS 1)



10 mL semisolid swallow with bolus residue (Consensus BRS 4)

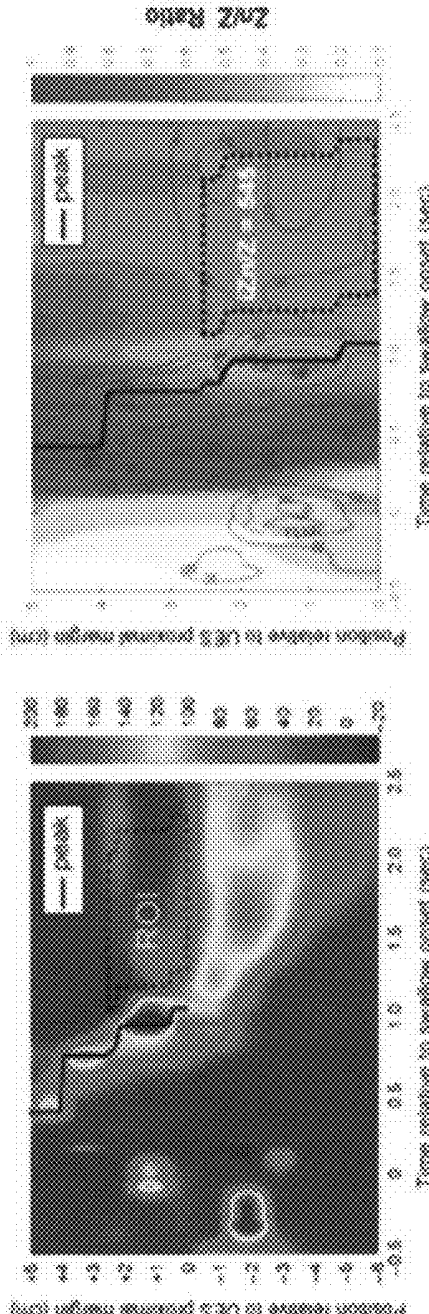


Figure 30

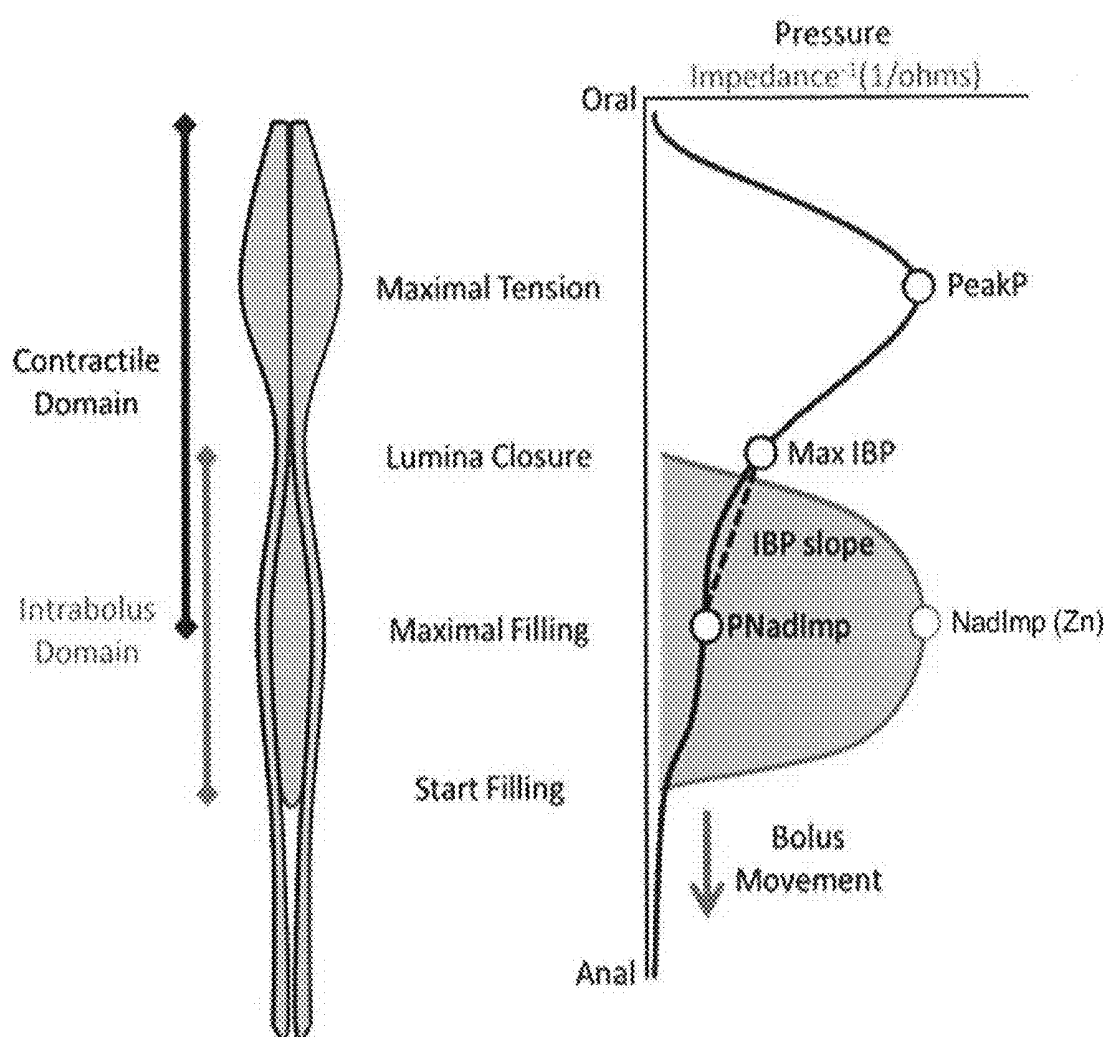


Figure 31

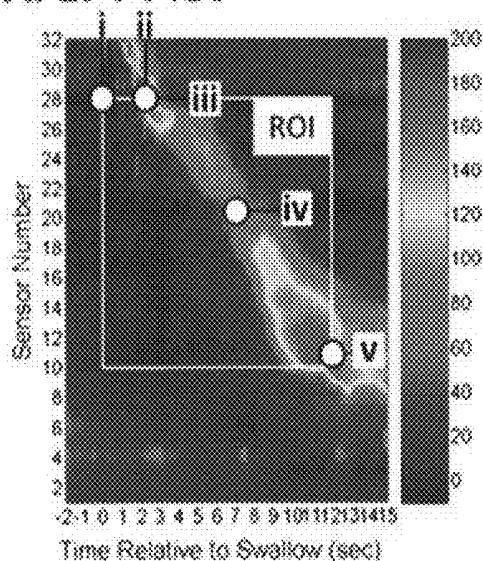
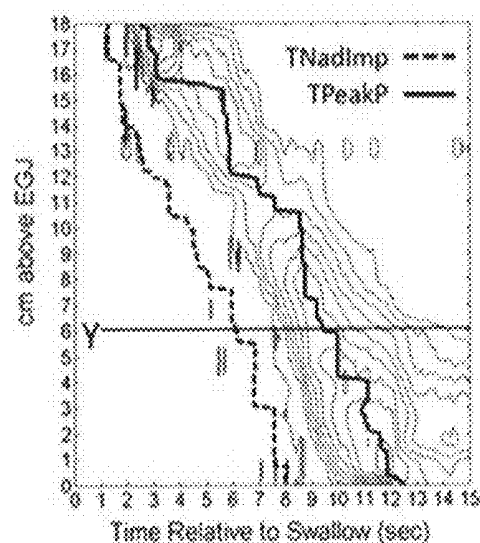
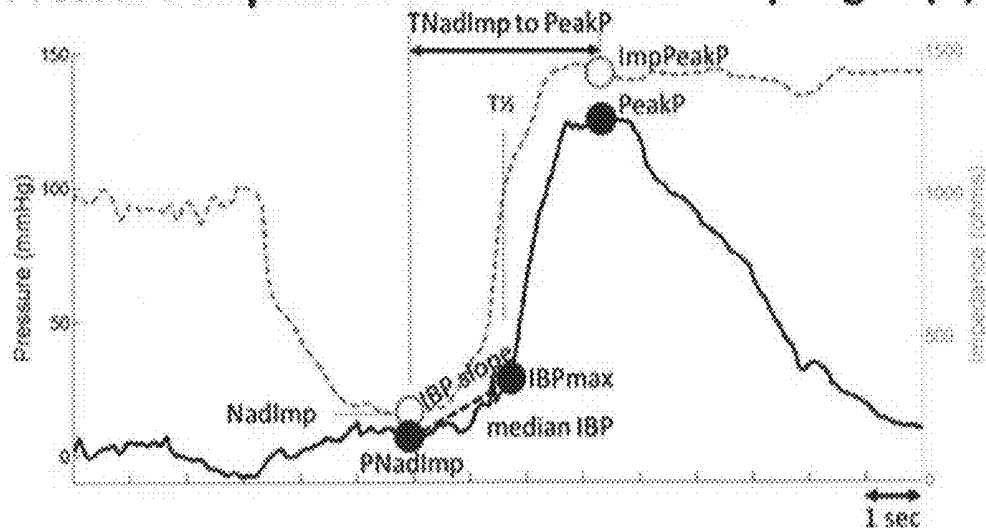
A. EPT Plot**B. AIM analysis plot****C. Pressure-Impedance at Mid Distal Esophagus (Y)**

Figure 32

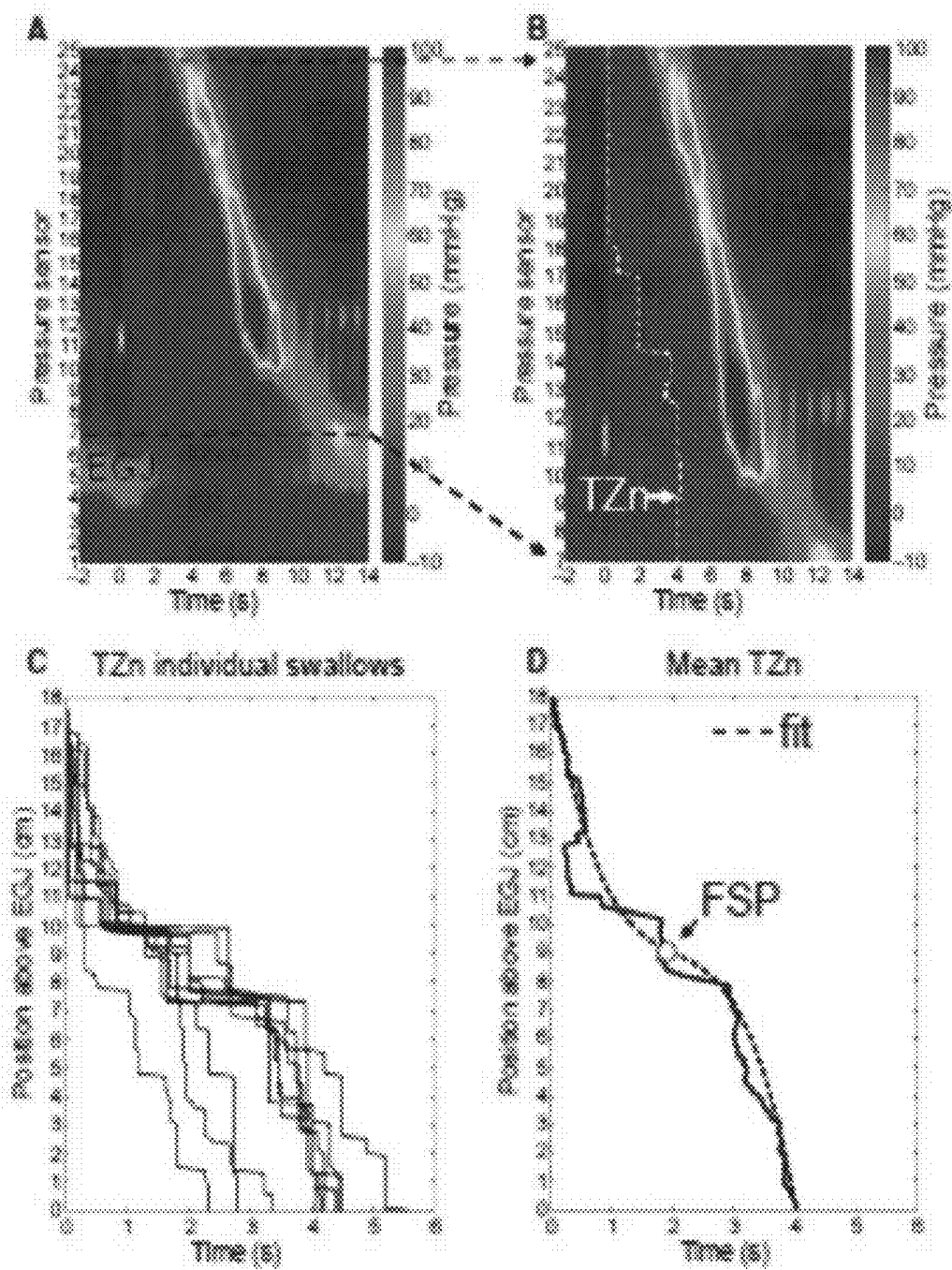


Figure 33

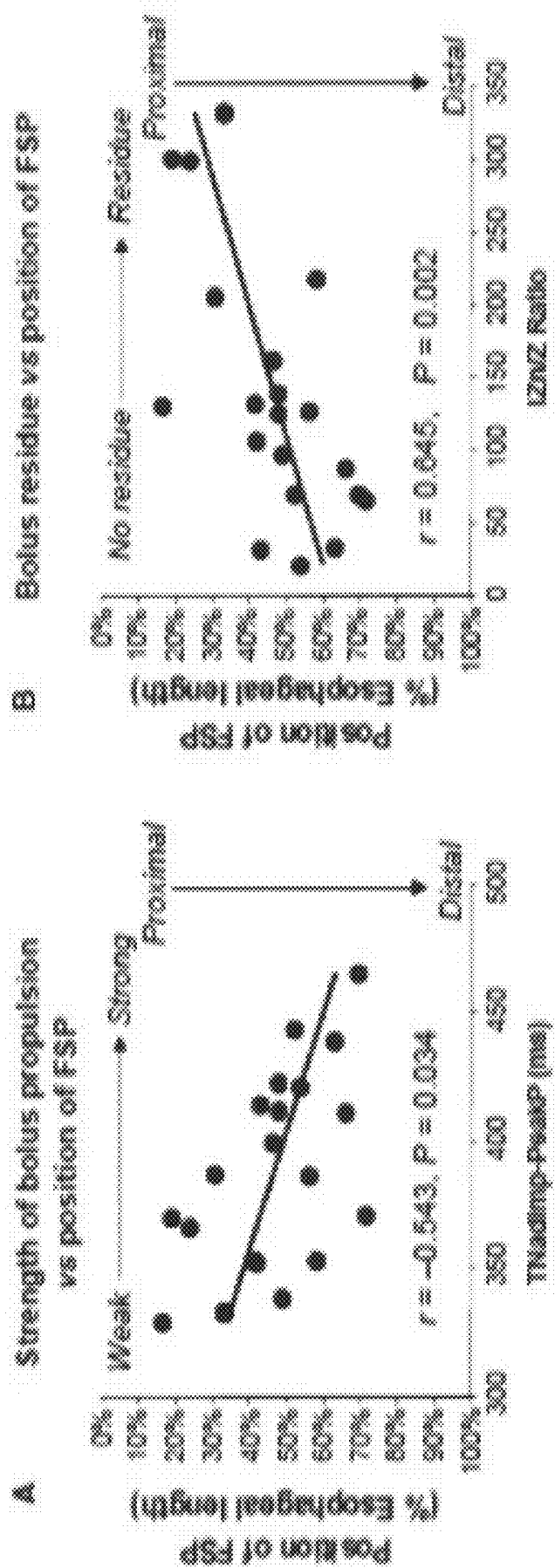


Figure 34

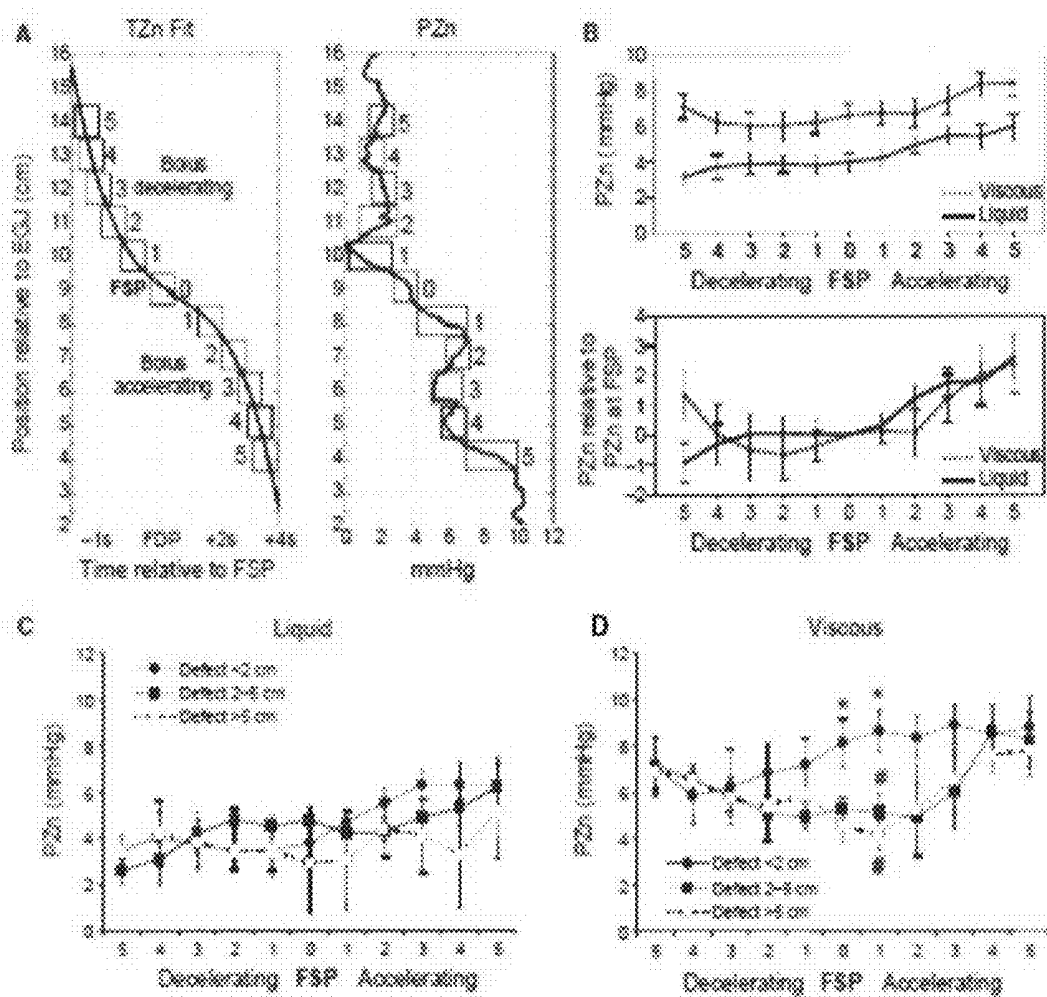
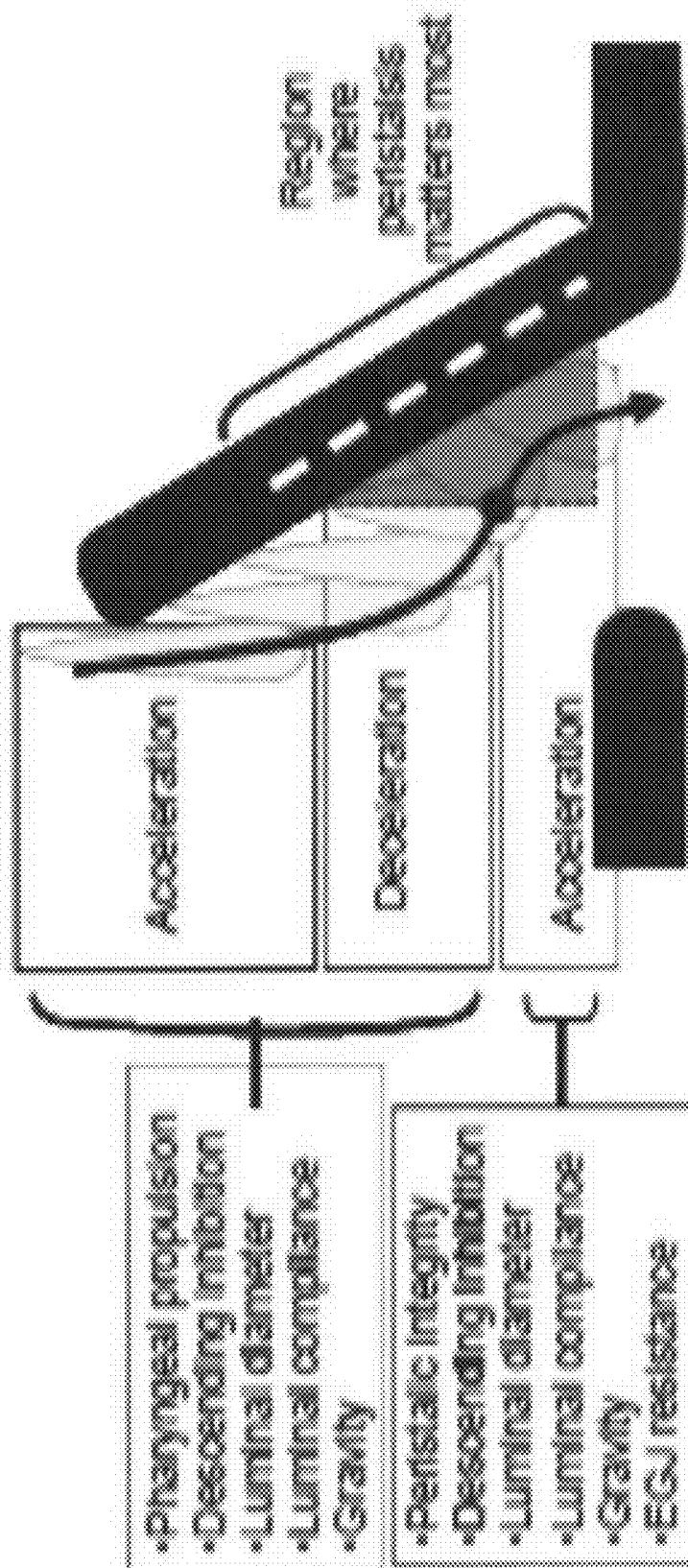


Figure 35



SWALLOWING MOTOR FUNCTION MEASUREMENT AND ASSESSMENT TOOLS, METHODS, AND APPARATUS

FIELD OF THE INVENTION

[0001] The present invention relates generally to tools, methods, and apparatus for assessing pharyngeal and/or esophageal motor function in a subject during swallowing. The measurements, tools, methods, and apparatus may be used to identify ineffective swallowing in the subject, including ineffective swallowing due to an obstruction, and may further be used to determine risk of aspiration in the subject.

BACKGROUND OF THE INVENTION

[0002] Swallowing is a complex process which involves a number of interdependent and coordinated phases. Generally, these phases include the preparatory, oral, pharyngeal and esophageal phases indicative of the anatomic regions traversed by a swallowed food and/or liquid bolus. During the preparatory phase, a food bolus for example remains in the mouth while it undergoes physical and some chemical changes which make it suitable for transit through the aerodigestive tract. During the oral phase, the bolus is propelled from the mouth into the pharynx by a peristaltic pressure wave generated by sequential squeezing of the tongue against the hard and soft palates. During the pharyngeal phase, the upper esophageal sphincter opens and the bolus is transported into the esophagus by a combination of peristaltic contraction of the pharyngeal constrictors and tongue movement continued from the oral phase. Finally, during the esophageal phase of swallowing, the bolus is transported further into the esophagus and stomach for digestion.

[0003] The portion of the swallowing process encompassing the oral to pharyngeal phases is often referred to as oropharyngeal swallowing. Oropharyngeal swallowing begins with closure of the vocal cords, signifying the activation of airway protection, and ends when the vocal cords return to their resting state. Indeed during this time, respiration is reflexively inhibited. Therefore, oropharyngeal swallowing serves two functions, namely transit of the bolus and protection of the airway, in which both functions are highly coordinated.

[0004] Due to the complex nature of the swallowing process, pharyngeal and esophageal motor function must operate effectively and in a coordinated manner for a successful swallow to occur. When motor function is compromised, difficulty in swallowing (dysphagia) arises and an ineffective swallow ensues.

[0005] Dysphagia is most commonly a consequence of a disease, disorder or condition which impairs coordination, or weakens swallowing biomechanics. For example, dysphagia is often associated with acute events, such as stroke, brain injury, and head and neck cancers, or arises as a result of surgery associated with such cancers. In addition, radiotherapy and chemotherapy associated with cancer treatment tends to weaken the muscles and degrade the nerves associated with the physiology and nervous innervation of the swallow reflex. It is also common for individuals with progressive neuromuscular diseases, such as muscular dystrophy and myasthenia gravis, to experience increasing difficulty in swallowing initiation. Dysphagia is also associated neurological conditions (such as cerebral palsy, Guillain-Barre syndrome, Huntington's disease, multiple sclerosis, Parkinson's

disease, and dementia), infectious illnesses, autoimmune illnesses, metabolic illnesses, myopathic illnesses, iatrogenic illnesses, and structural illnesses. Accordingly, dysphagia is generally considered an interdisciplinary phenomenon.

[0006] Dysphagia is often accompanied by aspiration due to ineffective airway protection during oropharyngeal swallowing. In effect, food particles, oral secretions and/or stomach contents become misdirected into the larynx and pass into the lungs. Pulmonary aspiration due to swallowing dysfunction (deglutitive aspiration) is the major reason for modification of feeding strategies (e.g. oral to tube feeding, avoidance of liquids etc.) which can significantly impact on the quality of life of affected subjects. Furthermore, aspiration can lead to recurrent pneumonia, progressive lung disease, and respiratory disability. Therefore aspiration is a serious condition which can, if undetected, result in severe complications and potentially death. Accordingly, dysphagia and pulmonary aspiration represent significant clinical, social, and economic costs and issues. For example, epidemiological studies estimate a prevalence rate for dysphagia of 16% to 22% among individuals over the age of 50. In addition, dysphagia is extremely common in the pediatric population within a wide range of disorders. This hinders the provision of adequate nutrition, affecting growth and development leading to significant parental anxiety and family disruption. Indeed, in the United States approximately 800,000 individuals per year are affected by dysphagia that is a consequence of neurological disorders, and stroke survivors alone can account for about 100,000 cases of aspiration.

[0007] Despite the significantly high prevalence of swallowing disorders and associated complications, the current methods for the assessment of swallowing and for the evaluation of direct aspiration are far from optimal. For example, manometry has been used to assess pharyngo-esophageal motor function in a variety of pathologies that cause pharyngeal weakness or impaired upper esophageal sphincter (UES) relaxation. Such disorders lead to ineffective pharyngeal bolus clearance and/or aspiration. The manometric technologies used for this assessment have evolved from single point pressure sensors, to movement-tolerant sleeve pressure sensors and, most recently, high resolution manometry which incorporates multiple closely spaced solid state point pressure sensors. These manometric methods have been utilized to describe the alterations in pressure patterns in relation to well recognized causes of aspiration. These include age-related changes, neurodegenerative disease, post-surgical dysfunctions, and abnormalities of the UES opening due to various factors. The use of manometry for assessment of aspiration risk has been very limited in routine clinical practice, because manometric criteria alone have not been shown to accurately assess risk of aspiration and/or post-swallow bolus residue.

[0008] Intraluminal impedance measurement has emerged in recent years as a technique that can be used to detect failed esophageal bolus transport. Intraluminal impedance measurement involves measuring impedance in real-time at multiple locations in the pharynx and/or esophagus, which can detect bolus movement through those organs. However, the application of impedance measurement to examine pharynx motor function has proven extremely challenging. Pharyngeal swallow events occur over a much shorter time span than esophageal peristalsis, and several factors cause large variations of the baseline level of impedance, such as variable mucosal contact, residue and secretions. These factors cause

impedance signals to be much more noisy in the pharynx than in the esophagus, so that attempts to optimize criteria that identify aberrant bolus flow events and residue have only been partially successful.

[0009] Fluoroscopic observation of pharyngo-esophageal bolus transit is the standard tool for evaluation of swallowing function and direct aspiration. Fluoroscopy is an imaging technique that uses X-rays to obtain real-time moving images of the internal structures of a patient through the use of a fluoroscope. However, the limitations of fluoroscopy are well-known, the most important of which include prolonged exposure to radiation and the qualitative nature of the test, because it is not possible to derive robust numerical measures. Accordingly it is not appropriate for patient screening. As a result, subjects who are potentially at risk of aspiration are often not referred for fluoroscopy until they have deteriorated clinically and present with weight loss, eating difficulties, recurrent respiratory infections or aspiration pneumonia. Whilst fluoroscopy can identify a point of narrowing of the lumen (such as a stricture, ring or web) that may be impeding normal flow of the bolus, in many patients the test fails to identify any obvious abnormality and these patient are often defined as suffering from non-obstructive dysphagia. Furthermore, even if used for patient screening, there is clear evidence that fluoroscopy is poorly predictive of progression to aspiration pneumonia, and due to limits on investigation time, a normal fluoroscopy cannot entirely guarantee the absence of feed aspiration.

[0010] Indeed, at present there is no method that is sensitive for identification of subjects at high risk for deglutitive aspiration at a time when aspiration-associated complications might be prevented by intervention. Even observed clinical signs and symptoms (such as wet voice, wet breathing, and cough) have only a 33-67% sensitivity to predict aspiration of liquids on fluoroscopy. Furthermore, fluoroscopy-based parameters, such as pharyngeal residue, are relatively poor markers of aspiration.

[0011] On the basis of the aforementioned inadequacies of existing techniques, there is a substantial interest in developing new and effective methods which enable an assessment of swallowing function in individuals, so as to identify those individuals with ineffective swallowing (for example due to a functional abnormality causing an obstruction), and who are therefore at risk of aspiration.

[0012] The foregoing examples of the related art and limitations related therewith are intended to be illustrative and not exclusive. Other limitations of the related art will become apparent to those of skill in the art upon a reading of the specification and a study of the drawings. Reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that this prior art forms part of the common general knowledge in any country.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings(s) will be provided by the Office upon request and payment of the necessary fee.

[0014] The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate some, but not the only or exclusive, example embodiments, implementation, and/or features. It is intended that the

example embodiments, aspects, implementation, and figures disclosed herein are to be considered illustrative rather than limiting. In the drawings:

[0015] FIG. 1 is a graph summarizing the subject cohort used for the studies described in Example 1. The graph shows the underlying medical pathology of each subject and the presence of aspiration-penetration as detected by videofluoroscopy.

[0016] FIG. 2 provides a series of graphs which show impedance (A) and pressure (B) measurements (represented as respective waveforms) derived from the passage of a bolus from the mouth to the esophagus of a subject. FIG. 2C shows how a combination of the impedance and pressure waveforms delineates four pharyngeal pressure-flow variables, namely PNadImp, Peak Pressure (PeakP), TNadImp-PeakP and Flow Interval.

[0017] FIG. 3 shows a series of iso-contour plots and graphs summarizing how the impedance and pressure measurements were analyzed to calculate the pharyngeal pressure-flow variables PNadImp, PeakP, TNadImp-PeakP and Flow Interval. (A) A pressure color iso-contour plot showing a first region of interest (1st ROI) used to calculate PNadImp, PeakP and TNadImp-PeakP, and a second ROI (2nd ROI) used to calculate Flow Interval. (B) Pressure impedance iso-contour plot for the 1st ROI showing the timing of pharyngeal nadir impedance and PeakP. (C) Graphical plots of TNadImp-PeakP, PNadImp and PeakP with average values shown. (D) Pressure impedance iso-contour plot for the 2nd ROI. (E) A graphical plot of maximum impedance (along y-axis of 2nd ROI) over time (x-axis of 2nd ROI). (F) Impedance cumulative time plot (derived using data in D) showing raw data, the third-order polynomial best fit and the inflection point of the best fit curve used to define the Flow Interval.

[0018] FIG. 4 shows graphs summarizing results of the analysis of combined impedance and pressure measurements and the pressure-flow variables that were significantly different in subjects compared to controls. (A) Peak Pressure (PeakP); (B) TNadImp-PeakP; (C) PNadImp; and (D) Flow Interval.

[0019] FIG. 5 is a box plot showing median and inter-quartile ranges for first swallow SRI in controls and subjects. Subject data are further stratified based on aspiration score. No aspiration=score 1, penetration=score 2-5 and aspiration=score 6-8. Grey circles show the data from individual swallows. Groups were compared using Kruskal-Wallis One Way Analysis of Variance on Ranks and Pairwise Multiple Comparison Procedures (Dunn's Method).

[0020] FIG. 6 shows graphs which establish that the first swallow SRI recorded in an individual subject can predict presence or absence of aspiration during fluoroscopy. (A) Correlation of patient average aspiration score with average first swallow SRI. (B) Kappa agreement between individual and average first swallow SRI cut-off values and the presence/absence of aspiration-penetration during fluoroscopy. Sensitivity and specificity curves for individual and average first swallow SRI are shown also in graphs C and D respectively. (E) Kappa agreement showing that a lower cut-off of SRI exhibited utility for defining post-swallow residue.

[0021] FIG. 7 provides a series of iso-contour plots showing that the pattern of abnormal pharyngeal and UES motor function in subjects varies with different pathologies that produce obstruction or weakness. Example tracings of first swallows (10 ml liquid) recorded in a control subject are shown in relation to three different pathologies (individual

results for pharyngeal variables and aspiration-penetration scores are shown in FIG. 8). (A) A 39 year old asymptomatic male control. (B) A 58 year old man who developed symptoms post anterior cervical fusion (C5-C6) surgery in whom fluoroscopy demonstrated high obstruction and no evidence of aspiration (aspiration-penetration score 1). (C) An 88 year old man with Dementia (Alzheimer's) and intermittent signs of aspiration on liquids in whom fluoroscopy demonstrated penetration (aspiration-penetration score 2). (D) A 57 year old stroke patient (male, right hemisphere) who had continuous signs of aspiration on liquids and in whom fluoroscopy demonstrated aspiration (aspiration-penetration score 7). Top row: iso-contour plots of pressure only. Second row: Pressure-impedance iso-contour plots showing pressure as lines (10 mmHg iso-contours) with impedance superimposed (iso-contour showing impedance levels <1 msu). Iso-contour plots of pressure within the dotted box are in the Third Row. In these plots dotted and solid lines define the timing of NadImp and the timing of peak pressure respectively.

[0022] FIG. 8 provides graphs summarizing a comparison of pharyngeal variables and aspiration-penetration scores for the four subjects for which data from sample individual swallows are shown in FIG. 7. Individual data for PeakP, PNadImp, TNadImp-PeakP, Flow Interval, aspiration-penetration score and SRI are shown, as is the patient average SRI for all (3-5) first swallows in each subject. Control ranges for each variable are shown by grey shading; abnormal findings compared to controls are indicated as black bars. For graphs comparing subject average SRI, the grey line indicates the optimal cut-off criteria.

[0023] FIG. 9 is a graph summarizing the pediatric patient cohort used for the studies described in Example 2. The graph shows the underlying medical pathology and presence of aspiration-penetration detected on videofluoroscopy.

[0024] FIG. 10 shows a series of iso-contour plots and graphs of pharyngeal swallow variables in a 9 year old male patient with cerebral palsy. In this patient aspiration-penetration was apparent during liquid swallows (average asp-pen score 3, range 1-8). This example swallow was given an asp-pen score 5 and the SRI was 41 and the average SRI for this patient was 20. (A) A pressure iso-contour plot showing region of interest 1 (ROI 1) used to calculate PNadImp, PeakP and TNadImp-PeakP and ROI 2 used to calculate Flow Interval. (B) Pressure impedance iso-contour plot for ROI 1 showing the timing of pharyngeal nadir impedance and peak pressure. (C) Plots of TNadImp-PeakP, PNadImp and PP with average values shown. (D) Pressure impedance iso-contour plot for ROI 2. (E) A plot of maximum impedance over time. (F) Impedance cumulative time plot showing raw data, the third-order polynomial best fit and the inflexion point of the best fit curve was used to define the Flow Interval.

[0025] FIG. 11 provides graphs showing agreement between pediatric patient average SRI cut-off criteria and the detection of aspiration-penetration during fluoroscopy. (A) Kappa agreement. (B) ROC curve.

[0026] FIG. 12 is a graph showing swallow risk index (SRI) calculations for subjects and controls used in the study described in Example 3. The SRI for all swallows was recorded in control subjects and dysphagic patients grouped according to the severity of residue based on anatomical location in the valleculae only (Val) or piriform sinus (PS) and/or posterior pharyngeal wall (PPW). Data presented as median [IQR], p-values shown for Kruskal-Wallis One Way

Analysis of Variance on Ranks of SRI. *p<0.05 for no residue vs. PS±PPW using Pairwise Multiple Comparison Procedures (Dunn's Method).

[0027] FIG. 13 is a receiver operator curve summarizing the predictive value of the swallow risk index (SRI) for determining the presence or absence of bolus residue. Receiver operator curves are based on SRI calculated for individual swallows as well as the average SRI determined for each individual. Numbers indicate data points corresponding to SRI values of 4-10.

[0028] FIG. 14 is a summary of the analysis methods used in the study described in Example 4. (A) A schematic of the catheter used showing the location of pressure ports and impedance electrodes. An example pressure isocontour plot of esophageal and EGJ pressures are also shown. (B) A combined pressure-impedance plot showing simultaneous recordings from pressure and impedance channels. Pressures shown as iso-contour lines, grey shading shows regions of low impedance indicative of the presence of bolus. The timings of NadImp and PeakP are marked at all positions down the plot. (C) A line plot of pressure and impedance recorded at 18 cm proximal to the EGJ. This illustrates how variables PNadImp, TNadImp-PeakP and Peak P are determined at all positions down the plot. (D) An expanded plot of C, illustrating how the IBP was determined at all positions down the plot.

[0029] FIG. 15 shows ROC curves for data obtained from the study described in Example 4 showing the baseline esophageal pressure-flow variables found to be significantly related to post-operative dysphagia.

[0030] FIG. 16 is a radiological image of subject 1 used in the study described in Example 5. The image was taken during swallowing and identifies a region of narrowing which is adjacent to the metal supports that have been implanted in the cervical spine of the subject.

[0031] FIG. 17 shows a series of plots and graphs summarizing how the impedance and pressure measurements taken from subject 1 of Example 5 were analyzed to identify an obstructed zone. (A) A pressure iso-contour plot of a 10 ml bolus swallow in subject 1 with the spatial region of the obstruction identified on the plot zone (between position -2 to -4 cm relative to proximal margin of UES). (B) A pressure impedance plot showing the spatio-temporal location of NadImp and Peak P. (C) A plot of TNadImp-PeakP, noting that TNadImp-PeakP is shortest between positions -2 and -6 cm (relative to UES proximal margin). (D) A plot of NadImp, noting that the level of NadImp is highest at position -2 cm (relative to UES proximal margin). (E) A plot of the "obstructive index" (NadImp/TNadImp-PeakP) which is highest precisely within the obstructed zone.

[0032] FIG. 18 shows a series of plots and graphs summarizing how the impedance and pressure measurements taken from subject 2 of Example 5 were analyzed to identify an obstructed zone.

[0033] FIG. 19 provides a series of representative graphs which show impedance (Z) and pressure (P) measurements (represented as respective waveforms) derived from the passage of a bolus from the mouth to the esophagus of a subject. FIG. 19A shows an example of a normal swallow, FIG. 19B is representative of ineffective bolus transport, and FIG. 19C shows an example of the change in pressure and impedance waveforms at the position of an obstruction. Changes in the values of Zn and ZPp are shown by arrows.

[0034] FIG. 20 provides a series of representative graphs which show impedance (Z) and pressure (P) measurements

(represented as respective waveforms in the left hand side of the figure) derived from five locations (1-5) along the length of the lumen as a bolus passes from the mouth to the esophagus of a subject. The boxed sections on the right of the figure show impedance values for Z_n and Z_{Pp} (measured in Ohms) at each of the five locations, and the value of Z_n/Z_{Pp} at each of the five locations. FIG. 20A shows an example of a normal swallow, FIG. 20B is representative of ineffective bolus transport, and FIG. 20C shows an example of the change in impedance values and Z_n/Z_{Pp} ratio at the position of an obstruction.

[0035] FIG. 21 provides results obtained from the analysis methods used in the study described in Example 6. Subjects with normal swallowing (A-C), failed (ineffective) esophageal bolus passage (D-F) and obstructed bolus passage due to aortic arch compression of the esophagus (G-I) are shown. A, D and G show iso-contour plots of pressures generated during the swallow. B, E and H show pressure-impedance iso-contour plots with pressure as lines (20, 30 and 50 mmHg iso-contours) and impedance superimposed (purple iso-contour showing impedance levels <0.5 msu). The timings of Z_n and Z_{Pp} are marked at all positions down the plots. Note that in E and H, retention of the bolus within the esophageal lumen after the peristaltic wave has passed is indicated by the impedance iso-contour which remains <0.5 msu (purple shading). C, F and I show graphs of values of Z_n , Z_{Pp} and Z_n/Z_{Pp} at all positions down the plots. Note that these real in-vivo recordings mirror the changes in Z_n , Z_{Pp} and Z_n/Z_{Pp} previously described in FIG. 20, whereby ineffective bolus passage (F in this Figure, B in FIG. 20) is indicated by an increase in Z_n and decrease in Z_{Pp} and obstructed bolus passage (I in this Figure, C in FIG. 20) is indicated when Z_n exceeds Z_{Pp} (i.e. $Z_n/Z_{Pp} > 1$).

[0036] FIG. 22 provides a series of scatter plots of mean values for Z_n max, Z_{Pp} max and Z_n/Z_{Pp} max obtained from 15 control subjects and 15 patients with non-obstructive dysphagia who demonstrated no evidence of obstruction on endoscopy and/or videofluoroscopy. (A) shows the average value of each subject/patient and average position of the max Z_n value relative to the Esophago-Gastric Junction (EGJ). (B) shows the average value of each subject/patient and average position of the min Z_{Pp} value relative to the Esophago-Gastric Junction. (C) shows the average value of each subject/patient and average position of the max Z_n/Z_{Pp} value relative to the Esophago-Gastric Junction. Note that in C four patients actually had a Z_n/Z_{Pp} of >1 ($\text{Log } Z_n/Z_{Pp} > 0$) which is suggestive of obstruction, even though obstruction was not detected using the standard tests.

[0037] FIG. 23 is a schematic diagram of an apparatus for assessing swallowing motor function.

[0038] FIG. 24 is a flow diagram of a method for assessing swallowing motor function in a subject n.

[0039] FIG. 25 is a flow diagram of a method for assessing swallowing motor function in a subject.

[0040] FIG. 26 is a flow diagram of a method for assessing swallowing motor function in a subject.

[0041] FIGS. 27A and 27B are topography plots of pressure Z and Z_n/Z ratios.

[0042] FIGS. 28A through 28E are graphical representations associated with the derivations and calculations of integrated Z_n/Z values.

[0043] FIG. 29 comprises topographic and isocontour plots illustrating derivations and calculations of integrated Z_n/Z values.

[0044] FIG. 30 is a diagrammatic illustration of a pharynx or esophagus region with a bolus in transit together with a correlated graph of pressures and impedances.

[0045] FIGS. 31A through 31C are graphic illustrations of NadImp, PNadImp, ImpPeakP, PeakP, median IBP, IBP slope, and IBP max variables on impedance-pressure plots.

[0046] FIGS. 32A through 32D are plots illustrating derivation of flow stasis point (FSP).

[0047] FIGS. 33A and 33B are graphical illustrations of correlations between flow stasis point (FSP) and other flow pressure variables.

[0048] FIGS. 34A through 34D are graphs illustrating measurements of pressure within a bolus (P_{Zn}) relative to flow stasis point (FSP).

[0049] FIG. 35 is a diagrammatic presentation of bolus trajectory pathway in an esophagus that illustrates a region where peristalsis matters most including the flow stasis point.

DESCRIPTION OF THE INVENTION

[0050] Accordingly, in a first example aspect a method for assessing swallowing motor function in a subject includes:

[0051] (a) accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;

[0052] (b) combining and analysing the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject; and

[0053] (c) assessing swallowing motor function in the subject by comparing the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.

[0054] In a second example aspect, a method for assessing swallowing motor function in a subject, the method including:

[0055] (a) accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;

[0056] (b) combining the intraluminal impedance and pressure measurements;

[0057] (c) generating a swallow risk index for the subject based on a combination of a value of more than one pressure-flow variable in the pharynx and/or esophagus of the subject, wherein the value is derived from an analysis of the combined intraluminal impedance and pressure measurements; and

[0058] (d) assessing swallowing motor function in the subject by comparing the swallow risk index for the subject to a predetermined reference swallow index.

[0059] In a third example aspect, a method for assessing swallowing motor function in a subject, the method including:

[0060] (a) accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;

[0061] (b) combining the intraluminal impedance and pressure measurements;

[0062] (c) generating an obstructive risk index for the subject based on a combination of a value of more than one pressure-flow variable in the pharynx and/or esophagus of the

subject, wherein the value is derived from an analysis of the combined intraluminal impedance and pressure measurements; and

[0063] (d) assessing swallowing motor function in the subject by comparing the obstructive risk index for the subject to a predetermined reference obstructive index.

[0064] In some embodiments of the aforementioned example aspects, the subject is suspected to have dysphagia.

[0065] By allowing an assessment of swallowing motor function in a subject, these methods may be used to identify a subject who has an ineffective swallow and is therefore at risk of aspiration. Therefore, in some embodiments these methods can be used to determine risk of aspiration in a subject, diagnose an increased likelihood of aspiration in a subject, predict aspiration in a subject, and/or identify a subject susceptible to aspiration.

[0066] As used herein, the term “ineffective swallowing” or “abnormal swallow” or similar terms is taken to mean a swallow which is associated with aberrant bolus flow, indicated by bolus material entering the airways, and/or is a swallow that results in the presence of post-swallow residue in the pharynx or esophagus. Accordingly, a “normal” swallow is a swallow which allows bolus to be transported from the pharynx to the stomach with insignificant or no bolus material entering the airways and little or no post-swallow residue.

[0067] As used herein, the term “swallowing motor function” should be understood to mean the coordinated physiological events that enable the passage of a food and/or liquid bolus from the mouth to the stomach. An assessment of swallowing motor function will typically involve an analysis of pharyngeal and esophageal motor function associated with the pharyngeal and esophageal phases, respectively, of the swallow. The pharyngeal phase is initiated as the tongue propels the bolus posteriorly and the base of the tongue contacts the posterior pharyngeal wall, eliciting a reflexive action that begins a complex series of events—the soft palate elevates to prevent nasal reflux; the pharyngeal constrictor musculature contracts to push the bolus through the pharynx; the epiglottis inverts to cover the larynx and prevent aspiration of contents into the airway; the vocal folds adduct to further prevent aspiration; the hyolaryngeal complex moves anteriorly and superiorly, which, in combination with the pressure generated by a bolus, provides anterior traction and intrabolus pressure to open the cricopharyngeus. In contrast, the esophageal phase is completely involuntary and consists of peristaltic waves that propel the food and/or liquid to the stomach.

[0068] Example tools, methods, and systems described herein include accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of a subject during attempted clearance of a bolus from the mouth and/or throat of the subject. As would be understood by a person skilled in the art, “clearance of a bolus” refers to the movement of a solid and/or liquid from the mouth and/or throat of a subject to the stomach.

[0069] It is to be made clear that the intraluminal impedance measurements and pressure measurements which are accessed for the methods of the present invention may be accessed from impedance and pressure measurements that have previously been obtained from the subject, and for example have been stored on a data/memory system, or the measurements may be obtained directly from the subject as a bolus clears from the mouth and/or throat of the subject (i.e.

in real-time). In the former case, the intraluminal impedance and pressure measurements are therefore obtained in isolation of, and therefore may or may not be part of the example tools, methods, and systems described herein.

[0070] Obtaining an “intraluminal impedance” measurement refers to detecting resistances and/or the occurrence of changes (during bolus passage through the pharynx and/or esophagus) in a resistance to electrical current across adjacent electrodes positioned in a serial manner along an axial length of the pharynx and/or esophagus in the gastrointestinal tract.

[0071] Intraluminal impedance may be measured in any suitable way, as would be understood by a person skilled in the art. For example, impedance may be measured by way of a narrow indwelling catheter upon which electrodes are longitudinally spaced. When the catheter is placed in the pharynx and/or esophagus the electrodes are in electrical contact with the luminal mucosa and/or with bolus, saliva, air, or other material in the pharynx or esophagus. Such catheters are routinely used for gastrointestinal investigations, most notably the detection and/or measurement of bolus movement downwardly or upwardly (retrograde) in the esophagus, and often used to detect, measure, or monitor the frequency and extent of gastro-esophageal reflux in patients with gastro-esophageal reflux disease. A high frequency electrical current is applied through consecutively connected impedance electrode pairs. The spaces between electrodes form linear segments along the catheter. The impedance to current flow for each segment is measured and stored in a sequential scan cycle fast enough to capture the impedance changes along the catheter during a swallow and/or during a reflux episode accurately. The current is generated and switched by external signal processing hardware and is applied across catheter electrodes via an electrical connector and wires to the electrodes on the catheter. In between swallows, the level of impedance recorded is proportional to the conductance of the luminal mucosa and is often considered to be a baseline impedance value for the subject. However, when a conductive bolus material (e.g. a swallowed bolus or a reflux bolus) passes along the catheter, this passage causes the measured level of impedance to drop across consecutive electrode pairs (due to the bolus material being more conductive than the mucosal tissue of the pharynx or esophagus adjacent to the electrodes). When the bolus material is cleared from the pharyngeal or esophageal lumen, the measured level of impedance returns to the baseline value for each impedance segment.

[0072] Impedance measurements may be captured electronically and recorded by a data acquisition system (of which there are many commercially available). Impedance patterns may be analyzed through the visual analysis of impedance graphs or curves derived from the impedance measurements to detect the occurrence of impedance levels and changes, with bolus presence defined by a drop of impedance, for example, to less than 50% of baseline levels. There are several semi-automated analysis software platforms that allow this analysis to be performed.

[0073] Obtaining a “pressure measurement” (also referred to as manometry) in the pharynx and/or esophagus refers to detecting the pressures and the occurrence of pressure changes (during bolus passage through the pharynx and/or esophagus) at sites in the pharynx and/or esophagus as a result of the contraction and relaxation of the pharyngeal and esophageal muscles during peristaltic movement of a bolus from

the mouth to the stomach. Static pressures due to bolus passage (intrabolus pressure) can also be measured.

[0074] In some example embodiments, pressure may be measured in the pharynx and/or esophagus via an indwelling catheter. As would be understood by persons skilled in the art, there are several methods for achieving such pressure measurements, including: (1) perfusion manometry—whereby a multi-lumen water-perfused catheter is introduced, with lumen vented in a longitudinal sequence along the catheter. The catheter lumen are perfused and intraluminal pressures are transferred to pressure transducers external to the catheter via the water in the catheter lumen; (2) use of solid state electronic (usually piezo-resistive) transducers which are mounted along the catheter, electrically isolated from the patient and connected to an external signal processing unit by wires within the catheter; (3) using optic fibre technology whereby deformation by pressure of a Bragg grating (etched onto an optic fibre) causes a change in the wavelength of light proportionate to pressure on the catheter; and (4) other methods utilized in commercial products including sensors measuring a change in capacitance as an analog of pressure and sensors using the deflection of an optic fibre due to applied pressure.

[0075] In some embodiments, both pressure and impedance can be recorded simultaneously by a catheter incorporating both pressure sensors and impedance electrodes. Examples of such catheters include those sold by Unisensor USA Inc, Portsmouth, N.H. In one embodiment, a 3.2 mm diameter solid state manometric and impedance catheter incorporating twenty five 1 cm-spaced pressure sensors and twelve 2 cm long impedance segments may be used. However, it would be understood by a skilled person that any method for recording pressure and impedance known in the art, whether conducted simultaneously or not, may be used.

[0076] It has been found that the combination of manometry data and impedance measurements indicating bolus position provide adjunctive information. When the two measurements are combined and properly analyzed together, they provide a more complete picture of swallowing motor function. Accordingly, use of the term “combining” in the context of this description is taken to mean that the impedance and pressure measurement data are analyzed and associated together so that one set of data is used to complement each other in analyses of swallow function and, in some examples, so one set of such data is used to guide analysis of or with the other.

[0077] This approach contrasts with the standard approach of evaluating impedance and pressure findings separately. For example, if impedance measurement detects failure of bolus clearance, the pressure measurement is then separately analyzed to determine a possible cause. Therefore, the term “combining” is not taken to mean that the data obtained from the impedance measurements is analyzed in isolation to the pressure measurement data and then both sets of data are combined to provide an assessment of swallow mechanics.

[0078] While manometry provides information about the contractile pressures that normally drive a bolus to the stomach, in certain situations, manometry alone may not provide sufficient information to fully assess bolus movement, particularly with respect to making a definitive diagnosis of certain disorders. By co-registering manometry and impedance data sets in both time and position according to the present invention, the interaction between contractile pressure and bolus movement during swallowing can be analyzed

in a precise and informative manner, and in a way that is not possible by analysing these two data sets independently. This approach enables a more reliable assessment of swallowing motor function.

[0079] Accordingly, the intraluminal impedance and pressure measurements are combined to derive a value or values for one or more pressure-flow variables in the pharynx and/or esophagus of the subject. The intraluminal impedance and pressure measurements may be combined such that in some example embodiments, the impedance measurements are used to guide analysis of the pressure measurements. Alternatively, in other example embodiments, the pressure measurements are used to guide analysis of the impedance measurements.

[0080] In some embodiments, analysis of the intraluminal impedance measurements includes the generation of an impedance waveform of the bolus clearance. Similarly, in some embodiments, analysis of the pressure measurements includes generation of a pressure waveform of the bolus clearance. As used herein, an “impedance waveform” or a “pressure waveform” are taken to mean the typical shape of a plot of impedance or pressure change over time. Impedance levels typically drop in relation to bolus presence and rise again with clearance of the bolus, hence the typical waveform drops below baseline impedance during bolus transit adjacent to an impedance segment of a catheter and then rises back to baseline impedance as the bolus clears away from such impedance segment. Pressure levels usually rise with luminal contraction near or onto a pressure transducer on the catheter and then drop when the contraction at that location subsides, hence the typical waveform rises from a baseline pressure then drops back to the baseline pressure.

[0081] As mentioned above, analysing the combined intraluminal impedance and pressure measurements may include derivation of a value or values for one or more pressure-flow variables in the pharynx and/or esophagus of the subject. As used herein, a “pressure-flow variable” is taken to mean a characteristic of the pressure waveform or impedance waveform or both wave forms (as is the case with timing variables) that are associated with swallowing motor function and are altered with pathology. A pressure-flow variable may be a characteristic of motor function of the pharynx and/or the esophagus during swallowing.

[0082] To derive a value for a pressure-flow variable, pressure and impedance measurements at a location in the pharynx or esophagus may be combined and analyzed by using characteristics of the impedance waveform obtained at such location, such as the time of its nadir (lowest point), as a time reference for direct measurement of pressure at such location, or to measure the interval of time to a pressure event at such location, such as the peak pressure of a pharyngeal/oesophageal contraction at such location. The absolute value of nadir impedance recorded in any location is related to the presence of bolus and the diameter of the lumen at such location, hence anatomical regions or locations of abnormal narrowing (such as strictures, webs, bars) may be identified by an increase in absolute impedance recorded at that location, for example, as compared to other locations during bolus transit. For example, the nadir of the impedance waveform at a location corresponds with when the lumen (pharynx or esophagus) is maximally distended/filled by a conductive bolus at that location. The nadir impedance of different channels (e.g., impedance segments) of the intraluminal impedance measuring catheter at various locations in the pharynx or esophagus can

be easily identified, thereby providing a point in time and space (location) at which useful pressure measurements can be measured and used. For example, combining and analysing the intraluminal impedance and pressure measurements may include determining and measuring the nadir of the impedance waveform for a particular location in the pharynx or esophagus, and wherein the nadir of the impedance waveform is used as a time marker for analysis of the pressure waveform at such location. In effect, the pressure at the nadir of the impedance waveform (PNadImp) represents one pressure-flow variable of swallow function. The pressure at nadir impedance is indicative of resistance within the pharyngo-esophageal segment with a higher pressure indicating more resistance.

[0083] From this impedance detected time point at a particular location, e.g., at a particular impedance segment (channel), the time interval to attainment of peak contractile pressure (Peak Pressure, PeakP, or Pp) of the pharynx or esophagus at that location can then be measured. The time interval from nadir impedance to peak pressure (TNadImp-PeakP) is a marker of swallowing efficiency with a shorter time indicating less efficiency. While manometry alone can reliably detect peak pressure, it does not reliably detect the time when the lumen (pharynx or esophagus) is maximally distended/filled. This time represents a reference time point that provides sensitivity to determining swallowing abnormalities. Therefore, the impedance, specifically, the impedance nadir in this example, is used to guide the determination of the initial time point for pressure measurement for this swallow efficiency analysis.

[0084] The pressure at the time of nadir impedance (pressure at nadir impedance) and the time from nadir impedance to peak pressure are pressure-flow variables obtained by analysing impedance and pressure measurements in combination that are useful for assessing swallowing motor function. The identification of nadir impedance to define a point in space and time to commence analysis for these pressure flow variables facilitates automation of analysis, thus providing a tool that simplifies and streamlines the determination, quantification, and assessment of swallow function. Computer-based algorithms can derive these and a variety of other variables referenced to this time. For example, the pressure at the mid-point of nadir impedance to peak pressure can be used to approximate intrabolus pressure, and the differential of this pressure and the pressure at nadir impedance can also indicate the slope (or “ramp”) of pressure increase, which is increased in the setting or location of an obstruction. As measurement is made along the entire pressure impedance array of the catheter extending partially or entirely through the length of the pharynx and/or esophagus, variables can be determined by averaging along the array or for regions corresponding to particular areas of interest, such as sphincteric regions (UES, LES) or the distal vs. proximal parts of the pharynx and esophagus.

[0085] Examples of pressure-flow variables which can be identified and quantified for swallow analysis and assessment tools as described herein include, but are not limited to, time of nadir impedance, value of nadir impedance, pressure at nadir impedance, time of peak pressure, value of nadir impedance preceding peak pressure, time from nadir impedance to peak pressure, peak pressure, value of impedance at the time of peak pressure, intrabolus pressure, intrabolus pressure slope, maximum intrabolus pressure, pressure at defined time points along the time interval from nadir impedance to peak

pressure (e.g., half time between), rate of pressure increase from pressure at nadir impedance to peak pressure (and time points between), ratio between the pressure at nadir impedance and the peak pressure, ratio between the nadir impedance preceding peak pressure and the impedance at the time of peak pressure, ratio between nadir impedance and impedance at other points in time for a location, integrated ratio between nadir impedance and impedance at other points in time for a region, and flow stasis point.

[0086] The “value” attributed to each pressure-flow variable will be dictated by the nature of the variable. For example, a variable associated with changes in pressure due to the passage of the bolus to the stomach will generally carry a value measured as a pressure unit, e.g., millimeters of mercury (mmHg). A variable associated with a particular time point or time period of the swallow will typically carry a time value, e.g., seconds (s), milliseconds (ms or msec), or other unit of time. A variable associated with impedance at particular points of time in bolus passage or at particular locations along the pharynx or esophagus will generally carry an electrical impedance value. Impedance values for some determinations and applications described herein, raw or direct impedance measurement units, e.g., ohms, are preferred and used. However, in some other determinations and applications of impedance values described herein, some kind of normalized impedance values may be beneficial. For example, baseline levels of impedance may vary greatly along the pharyngo-esophageal segment due to variability of mucosa to electrode contact and the presence of secretion or residue, so the standard approach to impedance analysis (time below/above variably defined thresholds relative to baseline) may be somewhat unreliable for some, but not all, purposes. Therefore, a method of impedance analysis was developed which analyzed the shape of the impedance waveform (as shown in FIG. 2 and explained below), rather than the magnitude of impedance change. In order to do this reliably, the raw impedance data were standardised to the median impedance (presented therefore as median standardised units (msu) rather than ohms). Some pressure flow variables may be some combination, formula, or ratio of two or more individual pressure flow variable, thus may have values comprising more than one of the units of measurement mentioned above or may be a number with no unit of measurement. The maximum, minimum, median, mode, average, and/or integration of any one or more of these variables for a particular location, for the entire array, or for an array corresponding to specific regions (UES, LES, proximal/mid/distal pharynx or esophagus) may represent a value for that pressure-flow variable.

[0087] According to one example implementation or aspect mentioned above, once the value of one or more pressure-flow variables has been derived from the combined intraluminal and impedance measurements taken from a subject, the value is compared to a predetermined reference value for that pressure-flow variable tool to facilitate quantitative assessment of some characteristic of the swallowing motor function in the subject. For example, the value of a pressure-flow variable derived from the combined analysis of measurements taken from the pharynx (or esophagus) of the subject are compared to a predetermined pharyngeal (or esophageal) reference value for that variable, the result of which is synonymous of some characteristic of the swallow function of the subject.

[0088] The value for each pressure-flow variable in a subject with a normal swallow will typically fall within a uniform

range, which may define or indicate a “predetermined reference value” for that variable. Accordingly, a value obtained from the swallow of a subject for that pressure-flow variable which falls some amount above or below the predetermined reference value, depending on how the values are defined and determined, will be an indicator of an abnormal or ineffective swallow in the subject, and/or will be an objective, quantified indicator of a risk of aspiration in the subject.

[0089] In some example embodiments or implementations, one of the pressure-flow variables is the pressure at the time of the nadir of the impedance waveform (PNadImp) at a location in the pharynx and/or esophagus of the subject. This pressure flow variable is a measurement the pressure in the pharyngeal and/or esophageal lumen when the bolus is being maximally propelled. Higher values of pressure at the nadir of impedance (PNadImp) correspond to resistance to bolus flow and/or ineffective bolus propulsion. Accordingly in one example embodiment, a higher PNadImp in a subject compared to a predetermined pharyngeal and/or esophageal PNadImp (ePNadImp) reference value is a quantitative indicator of ineffective swallowing in the subject, and/or it is a quantitative indicator of a risk of aspiration in the subject. With respect to the pharynx, the predetermined pharyngeal PNadImp (pPNadImp) reference value for a normal swallow in an adult is typically within the range of from 0 to about 26 mmHg such that a subject with a pPNadImp of about 27 mmHg or higher has a swallow with higher resistance to bolus flow and/or less effective bolus propulsion than a normal swallow, and such higher resistance or less effective bolus propulsion may predispose such subject to aspiration risk.

[0090] In some example embodiments or implementations, one of the pressure-flow variables is the peak pressure (PeakP) of the pressure waveform for a location in the pharynx and/or esophagus of the subject. For example, with respect to the pharynx, PeakP indicates contractile vigour of the pharyngeal stripping wave which clears bolus from the pharynx. A low PeakP is indicative of weak pressures, thus weak peristalsis for propelling a bolus. Accordingly, in one embodiment, a lower PeakP in the subject compared to a predetermined pharyngeal and/or esophageal PeakP reference value is a quantitative indicator of ineffective swallowing in the subject, and/or is a quantitative indicator of a risk of aspiration in the subject. With respect to the pharynx, the predetermined pharyngeal PeakP (pPeakP) reference value for a normal swallow in an adult is typically within the range of from about 93 to about 255 mmHg such that a subject with a pPeakP of about 92 mm Hg or lower has an ineffective swallow and/or risk of aspiration.

[0091] In some example embodiments or implementations, one of the pressure-flow variables is the time from the nadir of the impedance waveform to the PeakP (TNadImp-PeakP) in the pharynx and/or esophagus of the subject. For example, with respect to the pharynx, TNadImp-PeakP indicates the effectiveness of propulsion of the bolus (by the tongue) in advance of the pharyngeal contraction. A shorter TNadImp-PeakP is suggestive of weak propulsion. Accordingly, a shorter TNadImp-PeakP in a subject compared to a predetermined pharyngeal and/or esophageal TNadImp-PeakP reference value is a quantitative indicator of ineffective swallowing in the subject, and/or is a quantitative indicator of a risk of aspiration in the subject. With respect to the pharynx, the predetermined pharyngeal TNadImp-PeakP (pTNadImp-PeakP) reference value for a normal swallow in an adult is typically within the range of from about 371 to about 640

msec such that a subject with a pTNadImp-PeakP of about 370 msec or shorter has an ineffective swallow and/or risk of aspiration.

[0092] In some example embodiments or implementations, one of the pressure-flow variables is the duration of the drop in intraluminal impedance from baseline impedance during bolus clearance, which corresponds to passage of a bolus by an impedance segment (Flow Interval) in the pharynx and/or esophagus of the subject. Flow Interval is an estimate of the bolus presence at the location of a particular impedance segment of the catheter in the pharynx or esophagus before, during, and after the swallow. A longer Flow Interval in a subject compared to a predetermined pharyngeal and/or esophageal Flow Interval reference value is a quantitative indicator of ineffective swallowing in the subject, and/or a quantitative indicator of a risk of aspiration in the subject. With respect to the pharynx, the predetermined Flow Interval (pFlow Interval) reference value for a normal swallow in an adult is typically within the range of from about 100 msec to about 1250 msec such that a subject with a pFlow Interval of 1251 msec or longer has an ineffective swallow and/or risk of aspiration.

[0093] Other pressure-flow variables that provide some aspect of the pressure waveform or impedance waveform, either alone or in combination, that is associated quantitatively with a characteristic of swallow motor function may be used either in isolation or in combination with any one or more of the aforementioned variables PNadImp, PeakP, TNadImp-PeakP, and Flow Interval.

[0094] In some other example embodiments, or implementations, a value of more than one pressure-flow variable is combined to generate a swallow risk index in the subject, which is a quantitative indicator of the effectiveness of swallowing motor function in the subject, and which in turn enables the identification of an ineffective swallow and risk of aspiration in the subject. One example swallow risk index includes a ratio involving Flow Interval and/or PNadImp in the numerator and PeakP and/or TNadImp-Peak P in the denominator. For example, a swallow risk index that includes a ratio of the product of Flow Interval times PNadImp in the numerator and the product of PeakP times TNadImp-PeakP in the denominator provides a quantification that corresponds to swallowing motor function effectiveness and risk of aspiration, thus is a useful tool for assessing swallowing motor function of a subject as well as providing insight as to a risk of aspiration in the subject. Of course, persons skilled in the art would understand that inverting the numerator and denominator also provides a useful quantification for a swallow risk index, but the ratio value would be the reciprocal of the ratio value with the numerator and denominator as described above. Such variations are considered to be equivalent in function and usefulness. Persons skilled in the art would also understand that other variables or constants can also be included for particular quantifications to convenient values, for example, as illustrated in generating a swallow risk index (SRI) according to the following formula:

$$SRI = \frac{(\text{Flow Interval} \times \text{PNadImp})}{(\text{PeakP} \times (\text{TNadImp} \dots \text{PeakP} + 1))} \times 100$$

[0095] A swallow risk index generated in this manner that varies from a predetermined swallow reference index value is characteristic of an ineffective swallow and/or indicates a risk

of aspiration. For example, a swallow risk index generated as described above that is higher than a predetermined reference swallow index is indicative of an ineffective swallow and/or risk of aspiration in the subject. The “predetermined reference swallow index” essentially represents a swallow risk index value or range of swallow risk index values which are derived empirically from a subject or subjects with a normal swallow. Accordingly, such a swallow risk index which is higher than the predetermined reference swallow index value, or outside the predetermined reference swallow index value range, is an effective tool to identify and show an ineffective swallow and/or to indicate a risk of aspiration in the subject.

[0096] With reference to the above swallow risk index formula, when the value of each of the pressure-flow variables derived from the pharynx of an individual with a normal swallow is incorporated into the formula, a predetermined reference swallow index of between 0 to about 9 is obtained, and is therefore indicative of a normal swallow. In some example embodiments, a subject who has a swallow risk index of between about 10 to about 15 according to the formula will have post-swallow bolus residue indicative of an ineffective swallow. Furthermore, a subject who has a swallow risk index of about 16 or higher according to the formula is also at risk of aspiration.

[0097] From the description above, it should be appreciated that a swallow risk index may be obtained from any combination of pressure-flow variables identified by the methods of the present invention and which are quantitatively informative with respect to swallowing motor function. The swallow risk index need not be restricted to those variables identified in the formula above.

[0098] In some example embodiments, aspects, or implementations, a tool and method is provided to predict the occurrence of dysphagia in the subject following therapy and/or surgery. For example, a subject who has undergone surgery for the treatment of a gastrointestinal disorder (e.g., gastroesophageal reflux disease) will often develop post-operative complications due to restriction of the esophago-gastric junction. Furthermore, upper esophageal sphincter (UES) obstruction can occur following radio-therapy for head and neck cancer, following cervical surgery, in relation to neurological diseases such as cerebral palsy, or in relation to anatomical abnormalities (bars/strictures). In addition, esophageal body obstruction can occur in relation to the formation of strictures/webs which occlude the esophageal lumen. Obstruction of the UES or esophageal body, and restriction of the esophago-gastric junction are common causes of dysphagia, which is a difficulty in swallowing or a symptom of swallowing difficulty. Sufferers are sometimes unaware of their dysphagia.

[0099] The inventor has found that one or more pressure-flow variables derived or generated from intraluminal impedance and/or pressure measurements alone or in combination as described herein are useful tools that enable prediction of the occurrence of dysphagia in subjects which have undergone therapy and/or surgery for various diseases and conditions, including those described above. In one example embodiment, aspect, or implementation, one of the pressure-flow variables is intrabolus pressure (IBP) in the pharynx and/or esophagus of the subject. This intrabolus pressure variable (IBP) is a measure of the pressure required to move a bolus through the pharynx or esophagus. As illustrated diagrammatically in FIG. 30, a peristaltic muscle movement for propelling a bolus through the pharynx or esophagus is

characterized by a contractile domain where muscular tension in a contractile peristaltic wave tends to close the pharynx or esophagus lumen (lumina closure) behind the bolus. As the muscular tension of the contractile wave moves down the pharynx or esophagus (i.e., away from oral and toward anal), it pushes (propels) the bolus in that direction through the pharynx or esophagus. In FIG. 30, the contractile domain and the intrabolus domain are shown to overlap. Also in FIG. 30, a graphical representation of pressure and of impedance superimposed over each other is positioned alongside the net length of the contractile domain and the intrabolus domain. For visual convenience, the impedance curve is presented as the inverse of impedance so that one can visualize the increases and decreases in the contractile wave tension (e.g., pressure curve) in association with increases and decreases in lumen size as the bolus represented by the inverse of impedance curve moves through the pharyngeal or esophageal lumen. Therefore, in FIG. 30, the inverse impedance curve moves away from the baseline impedance where the bolus starts filling the pharyngeal or esophageal lumen and it returns to the baseline impedance as the bolus passes and the lumen closes. In FIG. 30, it can be seen that the pressure curve corresponds to muscular tension in and beyond the contractile domain and through the intrabolus domain. Concurrently, the inverse impedance curve above baseline impedance value corresponds to the bolus in spatial relation to the pharynx or esophagus and in relation to the contractile wave. The peak pressure (PeakP) point corresponds to the maximum contractile muscle tension in the contractile domain. The maximum intrabolus pressure (IBP max or max IBP) is the pressure at the time and point of lumen closure in the contractile domain and represents the tail end of the bolus domain, i.e., at the time and point where the bolus passes away as represented by the impedance returning to baseline impedance. The nadir impedance (NadImp) or (Zn) corresponds with the maximal fill of the pharynx or esophagus with the bolus. Because the curve is inverse of impedance, the nadir impedance point appears in the graph of FIG. 30 as the largest displacement of the curve from baseline, which facilitates envisioning the largest part of the bolus filling the pharynx or esophagus. The PNadImp point is the pressure at the time and location of the nadir impedance NadImp, i.e., where the bolus is widest and the pharyngeal or esophageal lumen is maximally filled. The IBP slope is the rate of change of pressure between the PNadImp and the IBP max, i.e., the rate of change of pressure in the bolus domain as the impedance returns from nadir impedance (NadImp) to baseline, which represents the change from a maximum filled lumen at a particular location or position in the pharynx or esophagus to closure of the pharyngeal or esophageal lumen when the bolus should have been propelled by the closing lumen away from that location or position toward the stomach. The closed lumen at that point of IBP max should also prevent retrograde bolus escape.

[0100] Amongst the individual metrics, IBP max and IBP slope appear to be the most significantly elevated in relation to greater perception of bolus passage, and they correlate strongly to bolus hold up. IBP increases in circumstances of resistance to bolus movement, for example following esophago-gastric junction (EGJ) restriction produced by fundoplication, which is a surgical procedure to treat gastroesophageal reflux disease (GERD) by narrowing and reinforcing the closing function of the lower esophageal sphincter (LES). Accordingly, in one example embodiment, aspect, or implementation, a higher IBP in a subject compared to a

predetermined pharyngeal and/or esophageal IBP reference value is a predictor for the occurrence of dysphagia in the subject following therapy and/or surgery. With respect to the esophagus, the predetermined esophageal IBP (eIBP) reference value is typically within the range of from 0 to about 12 mmHg such that a subject with an eIBP of about 13 mmHg or higher is predicted to be at risk of dysphagia, post-surgery.

[0101] In some example embodiments, aspects, or implementations, one of the pressure-flow variables is the intrabolus pressure slope (IBP Slope) in the pharynx and/or esophagus of the subject. As explained above, the intrabolus pressure slope (IBP Slope) variable is a measure of the rate of intrabolus pressure change over time. The rate of change of intrabolus pressure (IBP Slope) is elevated closer to an obstruction. Accordingly, in one example embodiment, aspect, or implementation, an elevated IBP Slope in the subject compared to a predetermined pharyngeal and/or esophageal IBP Slope reference value for a normal or healthy person is a useful tool for predicting the occurrence of dysphagia in the subject following therapy and/or surgery. With respect to the esophagus, the predetermined esophageal IBP Slope (eIBP Slope) reference value is typically within the range of from 0 to about 5 mmHg/sec such that a subject with an eIBP Slope of about 6 mmHg or higher is predicted to be at risk of dysphagia, post-surgery.

[0102] As also explained above, the IBP max variable is also strongly correlated to a bolus hold up. Therefore, in some embodiments, aspects, or implementations, an elevated IBP max in a subject compared to a predetermined IBP max reference value for a normal or healthy person is a useful tool in detecting bolus hold up and/or obstruction.

[0103] In some example embodiments, aspects, or implementations, one of the pressure-flow variables is time from the nadir of the impedance waveform to the peak pressure (TNadImp-PeakP) in the pharynx and/or esophagus of the subject. As discussed above, and with reference to the esophagus, this TNadImp-PeakP variable is a measure of the time interval from maximum bolus flow to esophageal contraction and is related to the speed and extent of bolus propulsion into the esophageal lumen balanced by resistive elements in the lumen that slow movement of the bolus. Accordingly, in one example embodiment, aspect, or implementation a shorter TNadImp-PeakP in the subject compared to a predetermined pharyngeal and/or esophageal TNadImp-PeakP reference value is a useful tool for predicting the occurrence of dysphagia in the subject following therapy and/or surgery. With respect to the esophagus, the predetermined esophageal TNadImp-PeakP (eTNadImp-PeakP) reference value for a normal or healthy person is in the range of from about 3.5 sec to about 8 sec such that a subject with an eTNadImp-PeakP of about 3.4 sec or less is predicted to be at risk of dysphagia, post-surgery.

[0104] Although the inventor has found that IBP, IBP Slope, IBP max, and TNadImp-PeakP are pressure-flow variables that are useful tools for predicting the occurrence of dysphagia in the subject following therapy and/or surgery, other pressure-flow variables generated by methods explained herein may also be useful in predicting dysphagia post-therapy and/or post-surgery.

[0105] FIGS. 31A, 31B, and 31C illustrate an example esophageal analysis, including the IBP Slope and the IBP max. FIG. 31A is an esophageal pressure topography plot showing pressures associated with an example 4 cm² bread bolus swallow. The X axis is time relative to swallow (e.g.,

sec), the left Y axis is the sensor number (i.e., associated with locations or axial positions in the esophagus), and the color scale is pressure (e.g., mmHg). Five space-time landmarks define the region of interest (ROI) for calculations. Those five space-time landmarks include the following: (i) The time of onset of swallow; (ii) The time of onset of proximal pressure; (iii) The proximal axial margin of the esophageal pressure wave sequence; (iv) The position of the transition zone from higher to lower pressures and then back to higher pressures; and (v) The distal axial margin of the esophageal pressure wave sequence.

[0106] FIG. 31B is a pressure isocontour plot of the region of interest (ROI) in FIG. 31A. The X axis is time relative to swallow (e.g., sec), and the left Y axis is distance above the esophago-gastric junction (EGJ) (e.g., in cm). The isocontour lines are pressure corresponding to the color scale in FIG. 31A for the ROI. FIG. 31B shows the bolus trajectory pathway (TNadImp), which identifies bolus passage relative to the esophageal pressure wave (TPeakP).

[0107] FIG. 31C is a pressure-impedance graph of the pressure and impedance data for the mid-distal location (i.e., position Y shown in FIG. 31B). The X axis is time (e.g., sec), the left Y-axis is pressure (e.g., mmHg), and the right Y axis is impedance (e.g., ohms). Key metrics (pressure flow variables) include, for example: Pressure at the time of nadir impedance (PNadImp) (e.g., mmHg); Peak pressure (PeakP) (e.g., mmHg); Median intrabolus pressure (IBP) (e.g., mmHg); Maximum intrabolus pressure (IBP max) (e.g., mmHg); Time interval between nadir impedance and peak esophageal pressure (TNadImp-PeakP) (e.g., sec); and Intrabolus pressure slope (IBP slope) (e.g., mmHg/sec). These metrics (pressure flow variables) are measured along the esophageal ROI using an automated software algorithm. As mentioned above, this tool and method is useful for detecting bolus hold up and/or obstruction which are predictors of dysphagia.

[0108] In some example embodiments, aspects, or implementations, the value of more than one of the pressure-flow variables that can be used to predict the occurrence of dysphagia in the subject following therapy and/or surgery may also be combined to generate a dysphagia risk index in the subject. For example, one or more of the IBP, IBP Slope, IBP max, and TNadImp-PeakP pressure flow variables discussed above may be multiplied by one or more other ones of those pressure flow variables to generate a useful dysphagia risk index that is a useful tool for predicting dysphagia in the subject post-therapy and/or post-surgery. One example of such a dysphagia risk index (DRI) has the following formula:

$$DRI = IBP \times IBP \text{ Slope} \times TNadImp-PeakP^{-1}$$

[0109] A dysphagia risk index generated as described above which is higher than a predetermined reference dysphagia index is a predictor for the occurrence of dysphagia in the subject following therapy and/or surgery. The “predetermined reference dysphagia index” essentially represents a dysphagia risk index value or range of dysphagia risk index values which are derived based on comparisons of dysphagia index risk values of persons with normal swallows to dysphagia risk values of a person or persons who develop dysphagia symptoms post-surgery and/or post-therapy so that the predetermined reference dysphagia index is such that a dysphagia risk index in a subject which is higher than the predetermined reference dysphagia index value, or which is outside the predetermined reference dysphagia index value range, is a predictor for the occurrence of dysphagia in the subject

following therapy and/or surgery. With reference to the above formula, the inventor has found that when the value of each of those pressure-flow variables derived from the esophagus of an individual with a normal swallow is incorporated into the formula, a predetermined reference dysphagia index of between 0 to about 14 is obtained, and is therefore indicative of an absence of dysphagia symptoms post-surgery and/or post-therapy. Accordingly, a subject who has a dysphagia risk index according to that formula of about 15 or higher post-surgery and/or post-therapy is predicted to be at risk of developing dysphagia. IBP max could be used instead of, or in addition to, IBP slope in the formula, but, of course the values of the dysphagia risk index and/or the predetermined reference dysphagia index might be different.

[0110] In one embodiment, the surgery is an anti-reflux surgery, for example Nissan Fundoplication, which is a surgical procedure to treat gastroesophageal reflux disease (GERD) and hiatus hernia in which the gastric fundus (upper part) of the stomach is wrapped or plicated 360 degrees around the lower end of the esophagus and stitched in place.

[0111] A dysphagia risk index may be obtained from any combination of pressure-flow variables generated by methods explained herein and which are informative with respect to swallowing motor function. The dysphagia risk index need not be restricted to those variables identified in the formula above or to such multiplication of such variables as in the formula above.

[0112] In some example embodiments, aspects, or implementations, the pressure measurements which are obtained from the pharynx and/or esophagus of the subject during clearance of the bolus from the mouth and/or throat of the subject can be used to guide analysis of the intraluminal impedance measurements. For example, pressure measurements obtained during the contractile wave can be used as a reference point to obtain an impedance value at any time in the contractile wave.

[0113] Accordingly, in some embodiments or implementations one of the pressure-flow variables is the nadir of the impedance waveform (Z_n) preceding peak pressure (PeakP) in the pharynx and/or esophagus of the subject. This variable is a measure of the impedance in the pharyngeal and/or esophageal lumen where the bolus is being maximally propelled in front of a contractile wave and with the lumen maximally distended by the bolus, i.e. prior to arrival of the pharyngeal and/or esophageal contractile wave. Higher values of the nadir impedance (Z_n) correspond to resistance to bolus flow, possibly due to luminal narrowing, and/or ineffective bolus propulsion. Accordingly, in one example embodiment or implementation, a higher Z_n in the subject compared to a predetermined pharyngeal and/or esophageal Z_n reference value is indicative of ineffective swallowing in the subject and risk of dysphagia due to bolus hold up. With respect to the esophagus, the predetermined esophageal Z_n reference value for a normal swallow in an adult is typically within the range of 0.001-0.027 median standardised units (msu) as derived from measurements of Z_n taken along the length of the esophagus during bolus transit. Still further, when the maximum value of Z_n (max Z_n) along the esophagus in normal subjects is considered, the predetermined esophageal Z_n reference value for max Z_n in an adult with a normal swallow is typically within the range of 0.002-0.031 median standardised units (msu). Therefore, a subject with a Z_n of about 0.025 or higher, or a max Z_n of about 0.03 or higher, has a swallow

with abnormal resistance to bolus flow and/or less effective bolus propulsion than a normal swallow which in turn may predispose to bolus hold up.

[0114] In some example embodiments, aspects, or implementations, one of the pressure-flow variables is the impedance at the time of peak pressure (ZPp) in the pharynx and/or esophagus of the subject. This variable ZPp is a measure of the impedance in the pharyngeal and/or esophageal lumen during the pharyngeal and/or esophageal contractile wave. Failure of a bolus to efficiently clear the pharyngeal and/or esophageal lumen will result in a low ZPp value, because bolus residue at an impedance segment of the catheter acts a conductor for current flow between the luminal electrodes that comprise the impedance segment where impedance levels are measured during swallowing.

[0115] During an ineffective swallow, the value of impedance at peak pressure (ZPp) will actually approach the nadir impedance (Z_n) that precedes peak pressure (PeakP). Accordingly, in one example embodiment or implementation, a lower ZPp in the subject compared to a predetermined pharyngeal and/or esophageal ZPp reference value is indicative of ineffective swallowing in the subject, and/or such lower ZPp will be indicative of a risk of bolus hold up in the subject. With respect to the esophagus, when the minimum value of ZPp (min ZPp) along the esophagus during bolus transport in normal subjects is considered, the predetermined esophageal ZPp reference value for min ZPp in an adult with a normal swallow is typically within the range of 0.188-0.779 median standardised units (msu). Therefore, a subject with a min ZPp of about 0.208 msu or lower has an ineffective swallow and/or risk of bolus hold up.

[0116] As indicated above, during an ineffective swallow ZPp will actually approach Z_n . As an extension of this relationship, when the pharyngeal and/or esophageal lumen is physically obstructed (either due to a zone of narrowing, or due to reduced luminal compliance which reduces the degree to which the lumen can distend/stretch to accommodate passage of a bolus) the reduced cross-sectional area increases the value of Z_n such that ZPp drops to below Z_n . This relationship is due to the presence of residue, thus low impedance, and the fact that the pharyngeal and/or esophageal contractile wave “bares down” upon the impedance segment of the catheter with much greater force than normal. Accordingly, in some example embodiments or implementations, a ZPp that is lower than the Z_n in the subject is the basis for a useful tool that shows objectively that an ineffective swallowing is due to an obstruction in the pharynx and/or esophagus of the subject.

[0117] As discussed above, postswallow residue is indicative of an impaired pharyngeal bolus clearance and is an indicator of interest when evaluating a dysphagic patient. For example, postswallow residue is indicative of impaired pharyngeal propulsion and/or increased resistance to flow at the upper esophageal sphincter (UES). A tool and method for direct detection of postswallow bolus residue includes a ratio between nadir impedance to impedance integrated over a region of interest (ROI) in the pharynx. One such ratio is the integrated nadir impedance to impedance ratio (iZ_n/Z), as will be explained in more detail below.

[0118] In one example implementation, to determine whether a subject has postswallow residue, a matrix of impedance values for the subject through the region of interest (ROI) in the subject's pharynx is used. As explained above, such a matrix typically involves a series of time-based impedance measurements at a plurality of axially spaced locations

or positions in the pharynx before, during, and after a swallow. Impedance catheters and measuring equipment for obtaining and recording such impedance measurements are well-known in the art, and persons skilled in the art know how to use such equipment to obtain such a matrix in the pharynx. A hypothetical example of such a matrix, which represents impedance (Z) values sampled at particular times (X axis) for each location or position of an impedance segment of the catheter along the longitudinal axis of the pharynx (Y axis), is shown in FIG. 27A in conjunction with a topography plot of the data in the matrix. The nadir impedance (Z_n) for each location is the lowest impedance value in the matrix for that location, e.g., the value 25 for each of the locations Y1 through Y5 in the hypothetical example of FIG. 27A. Then, Z_n/Z ratio data is created for each of the times in each location by dividing the Z_n value for each location by the impedance Z value at each time for that location. If x is the sample number, Z_n/Z ratio for that sample is $Z_n/Z \text{ ratio}_x = Z_n/Z_x$. Consequently, $Z=Z_n$ at a particular location, the Z_n/Z ratio at that location is 1. When Z is greater than Z_n at a particular location, the Z_n/Z ratio at that location is less than one. Since Z_n is by definition the nadir impedance for a location, Z is not expected to be lower than Z_n . A matrix of the Z_n/Z ratios for the matrix of hypothetical impedance values in FIG. 27A is shown in FIG. 27B along with a topography plot of the Z_n/Z ratios for that hypothetical. Values of Z_n/Z ratio residing within a particular post-swallow region of interest (ROI) in the pharynx are integrated in order to generate a single value reflecting the overall intensity of the Z_n/Z ratio, i.e., the integrated Z_n/Z ratio (iZ_n/Z) within that region of interest. An optimal region of interest (ROI) is the distal half of the pharynx, as will be explained in more detail below. Also, the region of interest (ROI) may be started at a time after the time of the pharyngeal contraction peak, so that the iZ_n/Z ratio is not influenced by pharyngeal compression of the catheter. For example, it may be started at 0.025 sec after the pharyngeal contraction peak and may have a duration of, for example, 1 sec.

[0119] An example of integrated Z_n/Z ratio calculation, based on individual channel (location) recordings at 1 cm proximal to the upper esophageal sphincter (UES) high pressure zone from 0.5 sec before to 2.5 sec after swallow onset of a normal swallow, is illustrated in FIGS. 28A through 28E. For each array (matrix) of impedance values, nadir impedance (Z_n) to impedance (Z) ratio was calculated and then values of Z_n/Z ratio residing within an optimal postswallow region of interest (ROI) were numerically integrated to generate a single value reflecting the overall intensity of Z_n/Z ratio, i.e., iZ_n/Z ratio, within the region of interest (ROI). FIGS. 28A, 28B, and 28C illustrate the calculation of Z_n/Z ratio at a single location in the pharynx during the time of a contractile wave of a swallow. In FIGS. 28A through 28C, the X axis is time (e.g., sec) relative to the swallow onset, and the Y axis is pressure (e.g., mmHg). FIG. 28A is a plot of only pressure for that location during the swallow, plotted from the swallow onset of a normal swallow, and shows the timing of the pharyngeal contraction peak, e.g., the peak pressure (PeakP). The raw impedance values at that location are shown along with the pressure values for that location in FIG. 28B. The nadir impedance Z_n is shown in FIG. 28B. To calculate the Z_n/Z ratio over time, the raw value of Z_n (FIG. 28B) was divided by all of the sampled raw values of Z (FIG. 28B) for that location, as explained in the hypothetical example above. FIG. 28C shows the Z_n/Z ratio values (right Y axis) in a curve

along with the pressure values (left Y axis) in a curve. At the time when Z equalled Z_n , the Z_n/Z ratio was 1, as shown in FIG. 28C, and at times when Z was greater than Z_n , the Z_n/Z ratio was less than 1, as also shown in FIG. 28C. Being reciprocal to impedance Z shown in FIG. 28B, the Z_n/Z ratio increases during the passage of the bolus and decreases when the bolus is cleared, as shown in FIG. 28C.

[0120] FIG. 28D is a pressure topography plot showing the anatomical location of the space-time landmarks used for this postswallow residue analysis example. The X axis of the plot in FIG. 28D is time relative to swallow onset (e.g., sec), the left Y axis is the position (location) relative to UES proximal margin (e.g., cm), and the right Y axis is pressure (e.g., mmHg). As mentioned above as shown in FIG. 28D, the optimal region of interest (ROI) in the pharynx is the distal half of the region from the velopharynx to the upper esophageal sphincter proximal margin in order to specifically identify residue within the area encompassing the piriform sinus, valleculae, and posterior pharyngeal wall, which are typical areas that may retain swallow residue. The midpoint between velopharynx and proximal margin of the UES high pressure zone was used to define the optimal position of the region of interest (ROI) in space. With respect to time, it is prudent to start the region of interest (ROI) enough after the pharyngeal contraction peak so as to not be influenced by compression on the catheter, and it is prudent to end the ROI sufficiently early so as to not be influenced by subsequent clearing swallows. A separate iterative evaluation of a range of start-times and durations for the postswallow ROI was performed (data not shown), and, based on that evaluation, it was determined that a ROI start time 0.25 sec after peak pressure and ROI duration of about 1 sec would be optimal, as shown in FIGS. 28D and 28E. To complete the analysis, the data array of Z_n/Z ratios within the area of the ROI (comprising 40 samples per second $\times$ 10 samples per centimeter mid-pharyngeal length in this example) was integrated (by cumulative trapezoidal numerical integration) to calculate the iZ_n/Z ratio value.

[0121] FIG. 29 shows example plots and iZ_n/Z calculations for swallows without and with bolus residue. The left plots in FIG. 29 are pressure topography plots in which the X axis is time relative to swallow onset (e.g., sec), the left Y axis is position (location) relative to UES proximal margin (e.g., cm), and the colors shading is pressure scales (e.g., mmHg). The right plots in FIG. 29 are isocontour plots in which the X axis is time relative to swallow onset (e.g., sec), the left Y axis is position (location) relative to UES proximal margin (e.g., cm), the right Y axis is Z_n/Z ratio, and which show the iZ_n/Z ratio for the ROI. The top two plots in FIG. 29 are for an example 10 mL semisolid swallow without bolus residue, and the bottom two plots are for an example 10 mL semisolid swallow with bolus residue.

[0122] In a study conducted by the inventors, the postswallow pharyngeal iZ_n/Z was evaluated as a potential correlated postswallow residue and there for predictor of ineffective swallowing. Optimal iZ_n/Z criteria were determined using a database of 50 randomly selected bolus swallows recorded with impedance, manometry, and videofluoroscopy. The iZ_n/Z was derived for a region of interest (ROI) spanning the midpoint of the pharyngeal stripping wave to the upper esophageal sphincter proximal margin, and from 0.25 to 1.25 seconds after the peak of the pharyngeal stripping wave. Videofluoroscopy was scored by four experts using a six-point bolus residue scale (BRS) score. Optimized criteria for iZ_n/Z were then applied to a much larger database of 225

swallows scored for residue by on expert observer. Among individual database, swallows iZn/Z was significantly correlated with average expert BRS score ($r=0.748$, $P, 0.0001$). An iZn/Z of greater than or equal to 500 was optimally predictive of swallows with residue defined by a BRS score of 4 or more. Within the larger cohort, iZn/Z was higher in dysphagia patient swallows compared with controls [2 (1, 4) vs. 1 (1, 3), $P<0.005$] and swallows with an iZn/Z greater than or equal 500 had higher bolus residue scores [4 (1, 6) vs. 2 (1, 4), $P<0.001$]. The Zn/Z was shown to be an easily determined objective non-radiological marker of clinically relevant postswallow residue and therefore an effective diagnostic tool for detecting postswallow residue and predictor for ineffective swallowing.

[0123] This approach of using intra-luminal impedance and manometry for direct detection of postswallow bolus residue is more successful than past attempts due to several factors. First, the nadir impedance provides a more reliable reference for standardization. Hence, by using the reciprocal of the measure impedance relative to the nadir impedance (i.e., Zn/Z), there is no longer a need to estimate pre-swallow impedance baseline which avoids the problems and complications from the inaccuracies associated with such estimates. Second, Zn/Z is measured within a specific region of interest of the distal pharynx defined by rigid space-time criteria. This procedure allows the assessment of residue to be made in a way that is least likely to be affected by either the primary pharyngeal contraction or secondary contractions related to clearing swallows. Third, the Zn/Z ratio data within the region of interest (ROI) are integrated over space and time to produce a single value of iZn/Z which defines the presence of postswallow residue in that ROI. Fourth, the calculation of iZn/Z is automated and objective by seamless incorporation into an existing analysis platform based upon three easily recognized landmarks, namely, swallow onset time, velopharynx position, and UES margin position. A positive iZn/Z is a direct marker of presence of postswallow residue and quantifies the degree of swallow dysfunction, which facilitates risk of aspiration. Also, a positive swallow risk index (SRI) as described above in combination with a positive iZn/Z as described herein provides strong objective evidence of deglutitive aspiration risk.

[0124] There is a benefit in using raw impedance values in this method and tool instead of, for example, the standardised median units described above. The nadir impedance Zn corresponds to the time when the lumen is maximally filled by a swallowed bolus. Therefore, Zn is used as a time reference point for the measurement of pressures using methods described herein. Theoretically, the absolute value of the nadir impedance should be influenced by luminal diameter. By using high-resolution plots of pressure, the measurement of impedance in time and space can be pinpointed precisely such that it corresponds precisely to the location of areas of interest, such as the upper esophageal sphincter (UES). We have been able to demonstrate that higher nadir impedance correlates with narrower diameter during UES maximum opening, which confirms what should be expected based upon theoretical first principles, whereby impedance of a filled chamber is inversely proportional to its cross-sectional area.

[0125] In some embodiments, aspects, or implementations, the values of more than one pressure-flow variable are combined to generate an obstructive risk index (ORI) in the subject. The value of the obstructive risk index in the subject is a tool that indicates whether the ineffective swallowing in the

subject is due to an obstruction in the pharynx and/or esophagus of the subject. For example, a ratio of Zn in relation to ZPp provides an effective and useful obstructive risk index for use as a tool to indicate whether an ineffective swallow is due to an obstruction. An example obstructive risk index (ORI) that includes such a ratio has the following formula:

$$ORI = Zn/ZPp$$

[0126] An obstructive risk index according to that formula which is higher than a predetermined reference obstructive index indicates that the ineffective swallowing is due to an obstruction in the pharynx and/or esophagus of the subject. The “predetermined reference obstructive index” for use in conjunction with obstructive index determinations according to that formula essentially represents an obstructive risk index value or range of obstructive risk index values which are derived according to the formula from a subject or subjects with a normal and/or unobstructed swallow. Accordingly, an obstructive risk index for a subject obtained with that formula which is higher than a predetermined reference obstructive index value, or which is outside the predetermined reference obstructive index range, is indicative of an ineffective swallow due to an obstruction in the pharynx and/or esophagus.

[0127] With reference to the above formula, when the value of each of the pressure-flow variables derived from the esophagus of an individual with an unobstructed swallow is incorporated into the formula, a predetermined reference obstructive index range of less than 1 is obtained, and is therefore indicative of an unobstructed swallow. In some embodiments, a subject who has an obstructive risk index of greater than 1 indicates that the ineffective swallow is due to an obstruction in the pharynx and/or esophagus of the subject. Of course, an inverse ratio of Zn to ZPp relationship, e.g., $ORI = ZPp/Zn$, when the value of each of the pressure-flow variables derived from the esophagus of an individual with an unobstructed swallow is incorporated into that inverse ratio, a predetermined reference obstructive index range of more than 1 is obtained, and is therefore indicative of an unobstructed swallow. Consequently, in some embodiments using that ratio in inverse, a subject who has an obstructive risk index of less than 1 indicates that the ineffective swallow is due to an obstruction in the pharynx and/or esophagus of the subject.

[0128] In some embodiments, aspects, or implementations, the obstructive risk index may be generated as a product of two pressure flow variables. For example, an obstructive risk index (ORI) may be generated according to the following formula:

$$ORI = NadImp \times TNadImp - PeakP^{-1}$$

[0129] With reference to this formula, if the lumen being distended is focally narrowed/obstructed then the rate of bolus flow through the narrowing and the bolus volume within the narrowing is reduced, which leads to the value of $NadImp$ rising and $TNadImp - PeakP$ becoming shorter within the narrowing. Accordingly, a subject with an obstructive risk index derived from the above formula which is higher than a predetermined reference obstructive index derived from this formula indicates that the ineffective swallow is due to an obstruction in the pharynx and/or esophagus of the subject.

[0130] It will be appreciated that an obstructive risk index may be obtained from any combination of pressure-flow variables identified by the methods of the present invention and which are informative with respect to the presence of an obstruction. The obstructive risk index need not be restricted to those variables identified in the formulae above.

[0131] Some example embodiments, aspects, or implementations may be used as tools or methods to identify the location of an obstruction along the pharynx and/or esophagus of a subject. For example, obstruction of the upper esophageal sphincter (UES) or esophageal body is common cause of dysphagia. As indicated above, such obstructions often occur following treatment for head and neck cancers, cervical surgery, in relation to neurological diseases such as cerebral palsy, and in relation to anatomical abnormalities (bars/strictures). Esophageal body obstruction can also occur in relation to formation of strictures/webs which occlude the lumen. Regardless of the cause, a tool or method that can identify the precise location of an obstruction may help guide interventions for obstruction (e.g., dilatation). In the pharynx, radiological imaging sometimes is unable to distinguish failure of UES opening due to obstruction versus failed UES opening due to poor bolus propulsion.

[0132] One or more pressure-flow variables derived from the methods of the present invention may identify the precise location of an abnormality/inefficiency which is causing an obstruction. For example, contraction of the pharyngeal and/or esophageal lumen moves the bolus toward the stomach. The pressure and impedance characteristics of the contractile wave will vary at a point in the lumen where an obstruction is present. Accordingly, in one embodiment, aspect, or implementation, one of the pressure flow variables is the maximum nadir of the impedance waveform preceding peak pressure (max Z_n) in the pharynx and/or esophagus of the subject during clearance of the bolus from the mouth and/or throat of the subject.

[0133] As indicated above, this variable corresponds with when the lumen (pharynx or esophagus) is being maximally propelled (i.e. maximally distended/filled by the conductive bolus). At the point where the lumen being distended is focally narrowed/obstructed then the bolus volume within the narrowing is reduced thereby leading to the value of Z_n recorded within the narrowing being higher (i.e. max Z_n) than the value of Z_n elsewhere in the lumen where no obstruction exists.

[0134] In some embodiments, aspects, or implementations, one of the pressure-flow variables is the minimum impedance at the time of peak pressure (min Z_{Pp}) in the pharynx and/or esophagus of the subject during clearance of the bolus from the mouth and/or throat of the subject. As indicated above, this variable relates to the impedance in the pharyngeal and/or esophageal lumen during the contractile wave. At the point where the lumen being distended is focally narrowed/obstructed then the failure of a bolus to efficiently clear the pharyngeal and/or esophageal lumen at this point will result in a lower Z_{Pp} value (i.e. min Z_{Pp}) than the Z_{Pp} values elsewhere in the lumen where no obstruction exists. Accordingly, the position of the min Z_{Pp} in the pharynx and/or esophagus of the subject is indicative of the position of the obstruction. Therefore, a tool or method that identifies the location of a max Z_n or a min Z_{Pp} is useful in identifying the location of an obstruction.

[0135] As indicated above, when the pharyngeal and/or esophageal lumen is physically obstructed, the reduced cross-sectional area increases the value of Z_n such that Z_{Pp} drops to below Z_n . Therefore, the position of the maximum Z_n/Z_{Pp} ratio as the bolus passes through the pharyngeal and/or esophageal lumen is indicative of the position of the obstruction. Accordingly, in some embodiments, the one or more pressure flow variables are the nadir of the impedance waveform pre-

ceding peak pressure (Z_n) in the pharynx and/or esophagus of the subject during clearance of the bolus from the mouth and/or throat of the subject, and the impedance at the time of peak pressure (Z_{Pp}) in the pharynx and/or esophagus of the subject during clearance of the bolus from the mouth and/or throat of the subject, and wherein the position of the maximum Z_n/Z_{Pp} in the pharynx and/or esophagus of the subject is indicative of the position of the obstruction.

[0136] In some embodiments, aspects, or implementations, one of the pressure-flow variables is time from the nadir of the impedance waveform to the peak pressure (TNadImp-PeakP) in the pharynx and/or esophagus of the subject. If the lumen being distended is focally narrowed/obstructed then the rate of bolus flow through the narrowing is reduced. This effect leads to the value of TNadImp-PeakP becoming shorter within the narrowing hence allowing the position of an obstruction to be identified.

[0137] Although the inventor has found that max Z_n , min Z_{Pp} , maximum Z_n/Z_{Pp} and TNadImp-PeakP, are pressure-flow variables, or combinations of pressure-flow variables, which can enable the position of an obstruction to be identified in a subject, any other pressure-flow variable (or combination of pressure-flow variables) which is also altered in relation to obstruction (and which has been identified by the methods of the present invention), can also be implemented to identify the position of an obstruction. Furthermore, these tools and methods can be used to identify obstructions in other regions of the gastrointestinal tract, such as the upper esophageal sphincter, lower esophageal sphincter, pylorus, duodenum, jejunum, ileo-cecal junction and colon.

[0138] As explained above, bolus transport from mouth to stomach relies on esophageal peristalsis, thus can be impeded by disordered or defective peristalsis or by abnormally high esophago-gastric junction (EGJ) pressures. 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, so it has been largely ignored in the context of the potential assistance pharyngeal propulsion may give to bolus transport. Prior to this invention, current understanding of human esophageal function in relation to bolus swallowing was based largely on pressure measurements performed concurrently with fluoroscopic imaging. The tools and methods described above utilize automated impedance-manometry techniques to detect and predict swallow dysphagia and risk of aspiration, including interactions between bolus transport and pressure generation within the pharynx. A keystone of that approach is the identification of timing of nadir impedance which can be used to track the trajectory of passage of the center of the bolus relative to the time of pressure generation, for example, at particular locations or positions. Similar techniques are used to assess the trajectory of bolus passage in the esophagus as will be explained in more detail below. In this explanation, reference is made to pressure flow variables, which provide certain indications as summarized in the following table:

Description of variable	What variable indicates
Pressure of the pharyngeal stripping wave	Pharyngeal contractile vigor Abnormal = low
Pressure at the time of nadir impedance (PZn)	Pressure within the pharyngeal bolus Abnormal = high

-continued

Description of variable	What variable indicates
Time from nadir impedance to peak pressure (TNadImp-PeakP)	Capacity to propel the bolus in advance of the pharyngeal stripping wave Abnormal = high
Flow interval	Bolus dwell time during swallow Abnormal = long
Ratio of nadir impedance to postswallow impedance (iZn/Z ratio)	Bolus residue Abnormal = high

[0139] Time of nadir impedance (TZn) during bolus swallow is used to track the trajectory pathway of the bolus head as it moves down the esophagus toward the stomach, as shown in FIGS. 32A and 32B. In FIGS. 32A and 32B, the X axis is time (e.g., sec); the left Y axis is the particular pressure sensors on the catheter in the esophagus, thus corresponding to particular positions spaced axially in the esophagus lumen; and the colors or shades are pressure (e.g., mmHg). Using the individual TZn curves from the respective pressure sensors for recorded swallows (FIG. 32C), the mean TZn curve is determined. In FIGS. 32C and 32D, the X axis is time, and the right Y axis is position above the esophago-gastric junction (EGJ) (e.g., cm). Typically, the TZn curve shows the bolus flowing rapidly, followed by deceleration, and then acceleration again as the bolus approaches the EGJ. 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, i.e., flow stasis point (FSP) is objectively determined from the mean TZn curve using the point of inflection of a third order polynomial best fit curve as illustrated in FIG. 32D. Persons skilled in the art know how to apply third-order polynomial best fit curves to data, so further explanation of that step is not necessary. The position of the flow stasis point (FSP) can be standardized relative to esophageal length which can be defined as the distance from UES distal margin to EGJ proximal margin measured during peristalsis. Pressures at nadir impedance (PZn) are 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 are 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 is assessed by measuring extent of the peristaltic wave with peak pressures less than 20 mmHg (called the 20 mmHg isocontour defect (20 mmHg IC defect)). The extent of EGJ relaxation is assessed using the average minimal integrated relaxation pressure for a 4 second interval or 4 second integrated relaxation pressure (IRP4 s).

[0140] Based on TZn curves in the example above, the estimated time from swallow to bolus reaching the EGJ was 3.3 plus or minus 0.2 seconds on average for liquid boluses and 4.7 plus or minus 0.3 seconds for viscous boluses (P less than 0.001. Pharyngeal PZn, flow interval, and integrated Zn/Z ratio (iZn/Z) were higher/longer and TZn to peak pressure (TNadImp-PeakP) was shorter for viscous boluses compared with liquid. Based on the location of the flow stasis point (FSP), liquid boluses were propelled farther along the length of the esophageal lumen than viscous boluses (FSP above the EGJ 7 plus or minus 1 cm versus 12 plus or minus

1 cm, respectively, P less than 0.005). The position of the FSP did not correlate with the position of the transition zone and was located on average 8 cm below the TZ for liquid and 3 cm below for viscous. The time from swallow to FSP was 1.6 plus or minus 0.01 sec for liquid and 1.7 plus or minus 0.02 sec for viscous boluses (ns). No significant correlations were observed with liquid boluses. However, for viscous boluses, shorter TNadImp-PeakP (FIG. 33A), longer flow interval, and higher iZn/Z (FIG. 33B) correlate significantly with the FSP being located higher in the esophagus. Although within normal limits, these data correlate a weaker pharyngeal function with a higher FSP. Esophageal variables did not correlate with FSP position.

[0141] FIGS. 34A and 34B show correlations of esophageal variables with PZn above the FSP. For both liquid and viscous boluses, pressure within the bolus increases at positions below the FSP. Correlation of esophageal variables and PZn at different axial positions relative to the FSP yield a relationship between increased distal esophageal pressures and increased PZn. Significant correlations were observed between 3 and 4 cm below the FSP for liquid boluses and FSP 2 cm below for viscous boluses. For viscous boluses, a correlation was observed between increased IRP4 s (i.e., reduced EGJ relaxation) and increased PZn at 4-5 cm distal to the FSP. No esophageal variable correlated with PZn above the FSP.

[0142] Larger 20 mmHg isocontour defect (20 mmHg IC defect), which is a measure of a zone of little or no propulsion where striated muscular tissue in the upper part of the esophagus transitions to smooth muscle tissue in the bottom part of the esophagus and shows where bolus transit slows down, correlated with lower PZn at or below the FSP (liquid $r=-0.539$, P less than 0.05 at 3 cm below the FSP; viscous at FSP $r=-0.548$, P less than 0.05 and 1 cm below $r=0.466$, P less than 0.05). This observation was explored further by comparing PZn for subjects with an average 20 mmHg IC defect less than 2 cm (i.e., complete peristaltic integrity, $n=10$) versus those with average IC of moderate size (2-3 cm, $n=7$) and large size (greater than 5 cm, $n=3$). The PZn for viscous boluses at FSP and 1 cm below was significantly lower in subjects with moderate-to-large peristaltic defects (FIG. 34C). There was no incremental difference apparent when comparing a defect size of 2-3 cm versus greater than 5 cm.

[0143] Bolus trajectory pathways measured in healthy subjects showed that time of nadir impedance has a typical trajectory curve with a pattern of bolus deceleration followed by stasis (inflection) and then acceleration. Bolus trajectory pathway can be described mathematically, which enables the FSP to be determined objectively. Furthermore, the pressure at TZn (i.e., PZn) measures the pressure within the bolus at maximum distention during bolus passage, as explained above in relation to FIG. 30. 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. Therefore, the esophageal body contractile amplitude may be least important prior to FSP and most important after the FSP. The shape of the bolus trajectory curve, from swallow onset to FSP is apparently driven by active force of pharyngeal swallow but also influenced by relaxation due to descending inhibition, passive luminal frictional forces, and gravity.

[0144] In this analysis and explanation, PZn is a measure of pressures within the bolus. While PZn is a hydrodynamic

pressure synonymous with intrabolus pressure, it 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 application is different from intrabolus pressure as previously applied, which was usually taken as the average/median pressure of the entire intrabolus domain. During the early part of the bolus trajectory curve (deceleration), PZn appears stable or gradually decreasing. During the latter part of the bolus trajectory curve (acceleration), PZn increases significantly as the bolus begins to move below the FSP. The pressurization 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. Measurements of FSP indicate that boluses for the most part slowdown 7-12 cm proximal of the EGJ even though the subjects are upright.

[0145] The 20 mmHg IC defect is a key diagnostic parameter when assessing esophageal dysphagia using clinical high-resolution manometry. 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. In patients with ineffective peristalsis leading to bolus retention, pressures within the bolus tail are significantly lower in the region of the transition zone. Consistent with these findings, we observed that PZn was lower at the FSP and below in subjects with moderate-severe IC defect compared with 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.

[0146] The correlation of higher PZn with higher peak esophageal pressures as described herein is 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. 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.

[0147] The objective and automated implementation of the method and tool for this measurement and analysis is a strength of this measurement approach and enables, for example, bolus driving pressures to be very reliably determined. This method provides an ability to describe the process of bolus transit using objectively measurable and automatically derived impedance-pressure variables, rather than the traditional method of pressure measurements combined with fluoroscopy, which involves a subjective observation of the fluoroscopic images that is not conducive to automation. Also, these new metrics of location and pressure in relation to bolus stasis as demarcated by the timing and location of the flow stasis point (FSP) is a switch from pharyngeal driven bolus transport to esophageal peristalsis driven bolus transport. Bolus flow along the esophageal lumen displays a typical bolus trajectory pathway characterized by bolus deceleration, stasis, and then acceleration again, as illustrated diagrammatically in FIG. 35. According to this tool and method, pharyngeal mechanisms determine the position of flow stasis while, at and below the FSP, the integrity of esoph-

ageal 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. As also illustrated in FIG. 35, the region immediately above, immediately below, and including the flow stasis point (FSP) is the region in the esophagus where peristalsis matters most in propelling and maintaining transport of the swallow bolus toward the stomach. Therefore, the FSP and these tools and methods for locating the FSP and for using the FSP in assessments of swallow motor function are important advancements in the field.

[0148] Various steps of the methods or implementations described above for determining and/or applying the pressure flow variables and tools described above may be performed in silico. For example, the intraluminal impedance and pressure measurements may be combined and analyzed by a computer software program, which may also have the capacity to derive a value for one or more pressure-flow variables. The program may also include instructions for assessing swallowing motor function by performing a comparison between the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.

[0149] Accordingly, the methods and tools described above can be implemented with software or firmware for use with a computer, e.g., a computer that includes a processor and associated memory for storing the software, wherein the software or firmware includes a series of instructions executable by the processor to carry implement the methods and tools as described above.

[0150] In another embodiment, aspect, or implementation, a computer readable media containing such software as described above can be provided.

[0151] In another embodiment, aspect, or implementation, apparatus for enabling an assessment of swallowing motor function in a subject includes:

[0152] (a) a processor;

[0153] (b) a memory; and

[0154] (c) software resident in memory accessible to the processor, the software executable by the processor to carry out a method or implement any of the methods or tools described above.

[0155] In another embodiment, aspect, or implementation, a computer readable media including a set of instructions in the form of a computer software program, the instructions being executable by a processing device on-board a programmed computer, wherein execution of the instructions causes the programmed computer to:

[0156] (a) accept, as an input, intraluminal impedance and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject;

[0157] (b) combine and analyse the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject;

[0158] (c) assess swallowing motor function in the subject by performing a comparison between the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables; and

[0159] (d) provide, as an output, an assessment of swallowing motor function in the subject on the basis of the comparison.

[0160] For example, execution of the instructions enables a computer process to proceed as follows. At the initiation of the computer process, intraluminal impedance and pressure

measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject are input. Input of the measurements can be performed manually by a user of the media, or the media itself may do this automatically once access to the measurements is enabled. The intraluminal impedance and pressure measurements are then combined and analyzed to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject. The value of the one or more pressure-flow variables is compared with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables, and an assessment of swallowing motor function in the subject is then made on the basis of the assessment. The assessment is provided as an output visible to a user of the media. The computer process then ends.

[0161] In one embodiment, the computer readable media further includes executable instructions which identify ineffective swallowing in the subject on the basis of the comparison. In some embodiments, the computer readable media further includes executable instructions which determine risk of aspiration in the subject, diagnose an increased likelihood of aspiration in the subject, predict aspiration in the subject, and/or identify a subject susceptible to aspiration. In some embodiments, the computer readable media further includes executable instructions which predict the occurrence of dysphagia in the subject following therapy and/or surgery. In some embodiments, the computer readable media further includes executable instructions which identify the position of an obstruction in the subject.

[0162] In another embodiment, aspect, or implementation, combination product includes:

[0163] (a) a device for obtaining intraluminal impedance and pressure measurements from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject; and

[0164] (b) software or a computer readable media as described above.

[0165] A device suitable for inclusion in the combination product according to an embodiment, aspect, or implementation described above is typically a catheter which incorporates both pressure sensors and impedance electrodes, as described above. It would be understood that the software, apparatus, or computer readable media may form an integral part of the device, or could be a separate entity to the device.

[0166] In some embodiments, aspects, or implementations, the subject is suspected to have dysphagia.

[0167] In some embodiments, the methods or tools described above may be useful for predicting curative therapy for aspiration or obstruction. For example, in the case of the pharynx, if the obstruction is localised to the upper esophageal sphincter, then this may contribute to aspiration. Knowledge of this may predict improvement with therapy (e.g. dilatation, myotomy, Botox). In the case of the esophagus, knowing the location of the obstruction allows the esophagus to be targeted by dilatation.

[0168] As used herein, the singular forms “a”, “an” and “the” include plural aspects unless the context already dictates otherwise.

[0169] Where a range of values is expressed, it will be clearly understood that this range encompasses the upper and lower limits of the range, and all values in between these limits

[0170] “About” as used in the specification means approximately or nearly and in the context of a numerical value or range set forth herein means $\pm 10\%$ of the numerical value or range recited or claimed.

[0171] The following examples are provided as illustrations of the methods, tools, apparatus, and systems described above, but they are not the only or exclusive ways to illustrate or implement the invention. It is to be understood that the following description is for the purpose of describing some particular embodiments only and is not intended to be limiting with respect to the above description.

Example 1

Assessment of Pharyngeal Motor Function Relevant to Aspiration—Adults

[0172] The aim of this study was to develop a new approach for the objective assessment of pharyngeal mechanical function relevant to aspiration. This used high resolution intraluminal manometry combined with impedance measurement (herein referred to as manometry and impedance). These data were explored for criteria that would enable recognition of individuals at high risk for clinically significant aspiration, without performance of fluoroscopy.

[0173] Methods

Subjects

[0174] Twenty subjects (13 male, mean 68.2 years, range 30-95 yrs.) were studied. These subjects had been referred to a swallowing clinic for a videomanometric study of the pharynx and esophagus because of clinical suspicion of deglutitive aspiration due to a deglutition disorder. Underlying diseases/conditions were identified through a review of medical records. The majority of subjects had a history of neurological disease or neurosurgery (FIG. 1). For comparison, ten healthy adult subjects (hereinafter “controls”) were recruited who had no swallowing difficulties and did not display other symptoms suggestive of a motility disorder (5 male, mean 36.6 years, range 24-47 years). The study protocol was approved by the Research Ethics Committee, University Hospitals Leuven, Belgium.

[0175] Measurement Technique

[0176] Studies were performed in the Radiology Department, University Hospitals Leuven with a 3.2 mm diameter solid state manometric and impedance catheter incorporating twenty five 1 cm-spaced pressure sensors and 12 adjoining impedance segments, each of 2 cm (Unisensor USA Inc, Portsmouth, N.H.). Subjects were intubated after topical anesthesia (lignocaine spray) and the catheter was positioned with sensors straddling the entire pharyngo-esophageal segment (velo-pharynx to proximal esophagus). Pressure and impedance data were acquired at 20 Hz (Solar GI acquisition system, MMS, The Netherlands) with the subject sitting. As per routine clinical fluoroscopy, test boluses of 5 and/or 10 ml liquid were administered orally via syringe. All bolus stock contained 1% NaCl. Video-loops of the fluoroscopic images of swallows were simultaneously acquired at 25 frames/second. The first swallow that followed bolus administration to the mouth was defined as the first swallow. If the first swallow failed to clear the bolus from the oral cavity, tongue-base, velliculae and/or piriform sinus, then the subject was asked to swallow again; these subsequent swallows were defined as clearing swallows. For controls, 8x10 ml liquid boluses were administered, 3 of these being recorded during fluoroscopy, which was the maximum allowed by the Research Ethics Committee, KU Leuven. The further 5 boluses were recorded with only manometry and impedance.

[0177] Fluoroscopic Assessment of Aspiration/Penetration

[0178] Fluoroscopic images from subject and control studies were scored for residue and for the occurrence of aspira-

tion-penetration without knowledge of the manometric findings. However, the subject/control status of the studies was not blinded, because, to the experienced analyst, subject swallows were for the most part distinguishable from the swallows of the control group. Aspiration-penetration was assessed using a validated 8-point score (Rosenbek J C et al., 1996, *Dysphagia* 11(2):93-98), influenced primarily by the depth to which material passes in the airway and by whether or not material entering the airway is expelled during the swallow sequence (Score 1=no aspiration, 2-5=penetration, 6-8=aspiration). Swallows were also assessed dichotomously for the presence or absence of post-swallow residue in the valleculae, piriform sinus and/or posterior pharyngeal wall.

[0179] Data Analysis

[0180] Manometry and impedance recordings were combined so as to correlate precisely in time with fluoroscopic images. The combined recordings were analyzed to derive four different pharyngeal pressure-flow variables indicative of timing and duration of maximal bolus flow, pressure during maximal bolus flow and pharyngeal contractile pressure. FIG. 2 illustrates manometry and impedance recordings represented as respective waveforms (FIGS. 2A and 2B), which when combined (FIG. 2C) delineate the four pharyngeal pressure-flow variables. Derivation of the variables is described in detail below.

[0181] Raw manometric and impedance data for each fluoroscopically observed swallow were exported from the recording system in ASCII text format and then analyzed by a separate computer using MATLAB (version 7.9.0.529; The MathWorks Inc). Pressure and impedance data were smoothed by a cubic interpolation method which doubled the temporal data and increased the amount of spatial data by a factor of 10 (pressure) and 20 (impedance), hence achieving a virtual increase from 1 pressure and 0.5 impedance values per 1 cm sampled every 5 msec (20 Hz) to 10 pressure and impedance values per cm sampled every 2.5 msec (40 Hz). As mentioned above, new method of impedance analysis was developed which analyzes the shape of the impedance waveform (as shown in FIG. 2), rather than the magnitude of impedance change, and the raw impedance data were standardised in this instance to the median impedance (presented therefore as median standardised units (msu) rather than ohms).

[0182] Pharyngeal Pressure-Flow Variables

[0183] From the pressure color iso-contour plot (FIG. 3A), two regions of interest (ROI) were defined. The 1st ROI demarcated the extent of the entire pharyngeal stripping wave for assessment of pressures along and relative to the stripping wave (see below). The 2nd ROI defined the region of the pharynx distal from the tongue base and was used to determine the pattern of impedance drop and recovery as a marker of bolus presence in the distal pharynx (see below).

[0184] 1st Region of Interest Analysis

[0185] The 1st ROI encompassed the spatial region from velopharynx to the proximal margin of the UES high pressure zone and the time interval from 0.5 sec before to 1.0 sec after swallow onset (FIGS. 3A and 3B). The timings of the pharyngeal impedance nadir (NadImp) and peak pressure (PeakP) were determined (FIG. 3B) at all positions along the 1st ROI. The average pressure at NadImp (average PNadImp), average PeakP and average time delay from NadImp to peak pressure (average TNadImp-PeakP) for the 1st ROI (FIG. 3C) were then calculated from these point data.

[0186] 2nd Region of Interest Analysis

[0187] The 2nd ROI encompassed the pharyngeal stripping wave from tongue-base to proximal margin of the UES high pressure zone; measurements were analyzed from 0.25 sec

before to 2.5 sec after swallow onset (FIGS. 3A and 3D). The interval/duration of impedance drop (Flow Interval) within the ROI was determined with a method based on one previously described for measurement of UES relaxation interval from pressure values recorded in the region of the UES high pressure zone (Ghosh S K et al., 2006, *Am. J. Physiol. Gastrointest. Liver Physiol.*, 291: 525-531).

[0188] The maximum impedances within the 2nd ROI were measured at all time points and plotted spatially (FIG. 3E). An impedance vs. cumulative time plot was derived by progressively increasing impedance thresholds from 0-2 msu in steps of 0.01 msu and determining the amount of time that the impedance was below each step level (FIG. 3F), this plot was then mathematically described using third-order polynomial equation (the typical equation for a curve with one inflexion). The cumulative time of the inflexion point of a smoothed best-fit curve was used to objectively calculate the flow interval (FIG. 3F).

[0189] UES Relaxation Variables

[0190] UES relaxation characteristics were measured using the established method of Ghosh S K et al., 2006 (supra) which objectively calculated UES relaxation interval (UES-RI), the UES nadir relaxation pressure (NadUESP), the median intrabolus pressure (median UES-IBP) and the UES resistance (calculated as NadUESP/UES-IBP).

[0191] Statistical Analysis

[0192] Non-parametric grouped data were presented as medians (inter-quartile range) and compared using the Mann-Whitney Rank Sum Test. For multiple comparisons Kruskal-Wallis ANOVA on ranks with pair-wise multiple analysis procedures (Dunn's method) was used. Correlation was determined using Spearman Rank Order Correlation. The association of variables with presence of aspiration was also assessed using Multiple Logistic Regression and ANOVA with Odds Ratio (95% CI). The sensitivities and specificities were determined for the different objective variables to detect of fluoroscopically defined aspiration. The level of concordance between criteria and the presence of aspiration was also expressed with Cohen's kappa Statistic. The scale for kappa values is: 0.00=no agreement, 0.00-0.2=slight, 0.21-0.40=fair, 0.41-0.60=moderate, 0.61-0.8=substantial, 0.81-1.00=almost perfect. For all tests a p<0.05 indicated statistical significance.

[0193] Results

[0194] In the subjects, 54 first swallows were evaluated with the three modalities of fluoroscopy, manometry and impedance. Of these, 28 swallows (in 17 subjects) failed to clear the bolus fully and in these subjects a further 40 clearing swallows were recorded. Deglutitive aspiration was observed during a total of 35 swallows comprising 14 first and 21 clearing (in 13 subjects). The median [IQR] aspiration score was 7 for these aspiration-associated swallows [5, 8]. Clearance failure was a weak risk factor for aspiration (odds ratio 1.24 [1.04, 1.48], p<0.05).

[0195] In controls, 26 first swallows were evaluated with the three modalities, and 47 were recorded without fluoroscopy. Of fluoroscopically recorded swallows, 8 (in 4 controls) exhibited trace amounts of residue and therefore failed to clear. Deglutitive aspiration-penetration was never observed during any fluoroscopically recorded control swallows.

[0196] First Swallows: Controls vs. Patients

[0197] Percentile charts for four swallow variables (based on First swallows) are shown in FIG. 4. Reference ranges (5th-95th percentile) for variables based on these charts are PNadImp: 0-26 mmHg; PeakP: 93-255 mmHg; TNadImp-PeakP: 371-640 msec, and Flow Interval: 100-1250 msec. For first swallows, UES-IBP and NadUESP were the only vari-

ables that were not significantly different in subjects compared to controls (Table 1). Patient first swallows with aspiration had a lower PeakP, longer Flow Interval, shorter TNadImp-PeakP and longer UES-RI than those without aspiration (Table 1; and FIGS. 4A, 4B and 4C). Patient first swallows with residue had a longer Flow Interval than those without residue (1290 [580, 2300] vs. 490 [320, 1120] msec respectively, $p=0.008$). Other first swallow variables were not different in relation to the presence/absence of residue.

TABLE 1

	PATIENTS			
	CON- TROLS All First Swallows	All First Swallows (p-value vs. CONTROL)	First Swallows WITHOUT Aspiration	First Swallows WITH Aspiration (p-value vs. NO Asp)
No.	72	54	40	14
Swallows Analyzed				
PeakP	138	99 (<0.001)	118	72 (0.018)
mmHg	[110, 178]	[66, 163]	[72, 193]	[28, 111]
P NadImp	12	21 (<0.001)	24	21 (0.547)
mmHg	[5, 17]	[13, 36]	[14, 53]	[13, 34]
Flow	320	800 (<0.001)	640	1980 (0.001)
Interval	[210, 590]	[470, 2090]	[340, 1300]	[1170, 2530]
msec				
TNadImp- PeakP	320	190 (<0.001)	260	50 (0.006)
msec	[210, 590]	[30, 300]	[100, 350]	[20, 160]
UES-RI	520	1030 (<0.001)	980	1250 (0.015)
msec	[400, 580]	[750, 1300]	[660, 1220]	[900, 1970]
UES-IBP	12	13 (0.311)	10	14 (0.453)
mmHg	[6, 20]	[9, 22]	[6, 24]	[9, 22]
NadUESP	6	5 (0.627)	5	5 (0.898)
mmHg	[1, 13]	[2, 10]	[2, 10]	[0, 13]
UES	22	13 (0.012)	14	9 (0.082)
resistance	[11, 41]	[8, 25]	[10, 26]	[4, 24]
mmHg/sec				

Summary data of 126 first swallows in controls and patients showing the relationships among important objective variables (pharyngeal variables shaded) and the presence of aspiration-penetration. Data presented as median [IQR]. P-values of Mann-Whitney Rank Sum Test for control vs. patient and no aspiration vs. aspiration shown in parentheses. Data for which $p < 0.05$ highlighted in bold text.

[0198] Fluoroscopically recorded control first swallows with residue had higher Peak Pressures (183 [137, 246] vs. 116 [95.6, 1334] mmHg respectively, $p=0.01$) and longer PNadImp-PeakP (0.47 [450, 510] vs. 400 [370, 450] msec respectively, $p=0.01$) than those without residue. The Flow Interval was not different during swallows with residue (320 [230, 560] vs. 300 [210, 380] msec respectively, $p=0.483$), neither were other first swallow variables, however, we noted that the variables most likely to be influenced by UES resistance were all evaluated in relation to residue (PNadImp 17 vs. 6 mmHg, $p=0.162$; UES-IBP 13 vs. 21 mmHg, $p=0.091$; NadUESP 16 vs. 8 mmHg, $p=0.128$; UES resistance 42 vs. 25 mmHg/sec, $p=0.162$).

[0199] Clearing Swallows: Subjects

[0200] Clearing swallows in subjects with aspiration had a longer Flow Interval than those without aspiration (2400 [2120, 2540] vs. 450 [380, 930] msec respectively, $p<0.001$). No other clearing swallow variables were significantly different in relation to aspiration. Subject clearing swallows with residue had a longer Flow Interval than those without residue (2240 [860, 2520] vs. 440 [390, 2060] msec respectively, $p=0.022$). Clearing swallows with residue also had a higher UES-IBP (20 [10, 28] vs. 12 [4, 20] mmHg respectively, $p=0.047$), a higher NadUESP (10 [5, 14] vs. 2 [1, 6] mmHg respectively, $p=0.007$) and higher DSR (26 [12, 34] vs. 14 [6,

21] mmHg/sec respectively, $p=0.049$). PeakP, PNadImp, TNadImp-PeakP and UES-RI were not significantly different in relation to residue.

[0201] Derivation of the Swallow Risk Index

[0202] Having observed that swallows in subjects with suspected aspiration have lower PeakP, higher PNadImp, longer Flow Interval and shorter TNadImp-PeakP than asymptomatic controls, we derived a swallow risk index (SRI) based on the following formula:

$$SRI = \frac{(\text{Flow Interval} \times \text{PNadImp})}{(\text{PeakP} \times (\text{TNadImp} \dots \text{PeakP} + 1))} \times 100$$

[0203] The overall median SRI for first swallows was significantly elevated in subjects compared to controls (17.4 [5.7, 59.6] vs. 1.7 [0.6, 3.7] respectively, $p<0.001$). Amongst swallows from the subject cohort, the median SRI's for swallows during which no aspiration was observed were lower compared to swallows with aspiration (First swallow SRI 11.9 [3.9, 21.3] without aspiration vs. 66.8 [24.6, 136.8] with aspiration, $p<0.001$; Clearing swallow mean SRI was 22.4 [10.5, 56.3] without aspiration vs. 64.9 [35.7, 105.2] with aspiration, $p<0.01$). Logistic regression also revealed that the odds ratio for the correlation of aspiration with SRI was 8.1 [2.0, 32.6] ($p=0.003$) for first swallows and 19.6 [2.3, 164.8] ($p=0.006$) for clearing swallows. The SRI increased significantly in line with increased severity of aspiration as is shown in FIG. 5 for first swallows. The median SRI also differentiated clearing swallows with penetration (22.4 [10.5, 56.3]) and aspiration 79.1 [49.3, 107.3], from clearing swallows with no aspiration (15.7 [5.8, 89.8]) (ANOVA $p=0.002$, pair wise $p<0.05$ aspiration vs. no-aspiration). Bolus volume had no significant effect on the SRI (First swallow SRI 23.0 [6.8, 72.4] vs. 15.9 [3.6, 24.6], $p=0.169$ and clearing swallow SRI 56.3 [22.4, 91.4] vs. 24.6 [12.8, 78.1], $p=0.267$ for 5 ml and 10 ml boluses respectively).

[0204] Predictive Value of First Swallow SRI

[0205] An assessment was performed to establish whether the first swallow SRI recorded in an individual subject could predict the presence/absence of aspiration during fluoroscopy. The average first swallow SRI correlated strongly with the average aspiration score for all fluoroscopically recorded swallows (Spearman Rank Order Correlation of 0.846, $p<0.00001$) (FIG. 6A). An average first swallow SRI of 15.0 was a perfect threshold for accurate prediction of aspiration in the patient cohort (FIG. 6B) and was also optimal in terms of sensitivity and specificity (FIGS. 6C and 6D) and Kappa (6E). As shown in FIG. 6E a lower cut-off of SRI exhibited utility for defining post-swallow residue.

[0206] Discussion

[0207] A novel automated approach to the analysis of pharyngeal manometry and impedance recordings was used to identify subjects with deglutitive penetration-aspiration. A swallow risk index was developed that is based upon the objective calculation of four pharyngeal pressure-flow variables. This new methodology is capable of identifying individual patients at deglutitive aspiration risk without use of fluoroscopy. The approach is based on the premise that the pathophysiology of deglutitive aspiration is multi-factorial. Hence, prediction of deglutitive aspiration risk requires the measurement of pressure and flow with high spatial resolution along the entire pharynx and the derivation of measures that assess the timing of bolus propulsion (TNadImp-PeakP), pressure during bolus flow (PNadImp), peak pharyngeal pressure and pharyngeal flow interval.

[0208] Previous approaches to the evaluation of the mechanics of pharyngeal bolus flow with pressure/impedance have only been partially successful. These prior studies concentrated on optimising impedance-based criteria, but the interpretation of the impedance signal is especially difficult in patients with suspected aspiration-penetration, because of pooling of secretions and altered motor function. The data presented above shows that incomplete pharyngeal emptying (i.e. residue after an initial swallow) is a relatively insensitive test on its own for patterns of motor function that result in aspiration-penetration (odds ratio 1.240, $p < 0.05$). Indeed, pharyngeal/UES motor function does not always empty the pharynx in healthy subjects, as the data from the control subjects presented above shows. The limitations of impedance recording have been addressed by the present study by strategies that extract more reliable information from the impedance signal, which was then used to guide the analysis of pharyngeal pressures. This approach achieved a more direct measure of the spatial organisation of pharyngeal motor function. This contrasts with the standard approach which evaluates impedance and pressure findings separately.

[0209] The combined manometry and impedance recordings were evaluated with automated analysis algorithms which derived the variables presented above. The entire impedance signal during swallowing was also analyzed automatically and processed in a way that reduced noise. This is a novel approach to evaluation of impedance signals which are usually scored according to periods of time during which impedance is above or below a certain cut-off value. Interestingly, the flow interval for first swallows was not elevated in relation to the presence of residue in controls, and, whilst elevated with residue in affected subjects, correlated more strongly with aspiration-penetration (OR 3.3 [1.5, 7.4], $p = 0.004$) than bolus residue (OR 2.4 [1.1, 5.2], $p = 0.021$), suggesting that the flow interval is a very useful single measure of deglutitive function/dysfunction. However, flow interval alone cannot in itself diagnose the cause of dysfunction, hence the importance of inclusion of other direct measures. As illustrated in FIGS. 7 and 8, the pattern of abnormal pharyngeal and UES motor function in subjects varies with different pathologies that produce obstruction or weakness. For example, obstruction subject B, compared to dementia and stroke subjects C and D, had a normal PeakP but elevated PNadImp. Stroke subject D had a mean TNadImp-PeakP < 0 (i.e. on average nadir impedance occurred after peak pressure) this is suggestive of highly ineffective bolus propulsion in advance of the pharyngeal stripping wave. Dementia and stroke subjects C and D had the highest SRI, consistent with fluoroscopy findings of penetration and aspiration respectively.

[0210] Because the SRI takes into account several different measures of function, it delivers an accurate assessment of aspiration risk regardless of the pattern of functional impairment. Recognition of particular patterns of impairment of pressure-flow variables should allow a relatively specific diagnosis of varying swallow mechanical dysfunctions that result in aspiration. From such analysis, it may be possible to devise well targeted therapeutic interventions.

[0211] The automated and objective methods used for deriving pharyngeal pressure-flow variables is a major strength of this study. Though these methods are complex in themselves, they are simple to apply, since the operator only needs to define the region of interest on the specially developed analysis system. This new method receives the data directly from high resolution manometric systems as text, a standard output of such equipment.

[0212] This study also evaluated UES relaxation pressure-time variables (UES-RI, NadUESP, UES-IBP and UES resistance). Whilst UES-RI and UES resistance were significantly different in our subjects, only UES-RI was significantly altered in relation to the presence of aspiration-penetration. This is an interesting finding, given that the most frequently used interventions for aspiration, UES myotomy and Botulinum toxin injection, are aimed at weakening the UES. Such interventions are however known to have inconsistent efficacy in subjects with CNS damage who represent the majority of the subjects in our study cohort. Undoubtedly there are subjects who have problems with aspiration-penetration because of impaired UES opening, but these were not well represented in the cohort.

[0213] In the present study, the analysis of a large number of variables recorded with very high time resolution from the manometric and impedance tracings would have been impossible without automation. This wealth of variables that were measured allowed the exploration of which combinations of variables were most effective for identifying subjects with aspiration-penetration, hence the derivation of the SRI. The results of the present study showed that average data from as few as 3-5 first swallows are sufficient for determining a reliable estimate of a subject's aspiration risk.

[0214] The present studies were all performed using topical anaesthesia. Topical anaesthesia is important for providing a level of comfort so that the procedure can be performed quickly and effectively. Used judiciously, mucosal anaesthesia appears to have had no effect on the outcomes, given the large differences seen between subjects and controls and swallows with or without aspiration. Other possible factors that may have influenced our findings are the fact that our control group were relatively young compared to the subject group. This is relatively unimportant as our major analysis and conclusions with respect to aspiration are based upon exploration of data from subjects only. The subject cohort of the present study predominantly had neurological diseases but was nevertheless varied and included subjects with a wide age range. The subjects were studied prospectively as they were referred for investigation and therefore there was no control over which subjects were to be investigated in the present study. This study design means that the cohort is typical of the overall population of subjects in whom aspiration is suspected on clinical grounds.

[0215] The fact that the predictive value of the SRI appears to be robust in the face of the potential confounding factors discussed immediately above engenders confidence that this methodology has very real potential for clinical implementation as a screening tool for aspiration risk. There are many populations at risk for aspiration-penetration, such as post-stroke subjects, subjects with diverse neurological and muscle diseases or those who have had pharyngeal or neurological surgery. These subjects are well represented in the study cohort and demonstrated elevated SRI in relation to aspiration. These subjects are most often not investigated by fluoroscopy until they demonstrate clinical signs and symptoms of aspiration. The value of using this methodology as a screening tool to trigger early intervention requires further investigation by way of outcome studies to determine if, for example, SRI predicts clinical deterioration and what interventions are of most value.

[0216] In conclusion, the present study provides novel findings in control subjects and in a cohort of subjects with predominantly neurological problems who were referred for investigation of suspected aspiration. These show that combined high resolution solid state manometry and impedance recordings can be objectively and automatically analyzed to

derive robust multiple pressure-flow variables that are altered in relation to pathology. Importantly a swallow risk index can be derived through the combination of these pressure-flow variables and used to predict circumstances when aspiration is likely.

Example 2

Assessment of Pharyngeal Motor Function Relevant to Aspiration—Children

[0217] The aim of this study was to apply the approach developed in Example 1, i.e. the use of high resolution intraluminal manometry combined with impedance measurement, for the objective assessment of pharyngeal function relevant to aspiration in infants and children. This approach was evaluated to determine if it enables recognition of pediatric patients at high risk for clinically significant aspiration, without performance of fluoroscopy.

[0218] Methods

Subjects

[0219] Eleven pediatric dysphagic patients (mean 6 years, range 5 months-13.4 years) were referred for a videomanometry study of the pharynx and esophagus. Underlying diseases/conditions were identified through a review of medical records. The majority of patients had a neurological history (FIG. 9).

[0220] Measurement Technique

[0221] All fluoroscopy studies were performed in the Pediatric Radiology Department, University Hospitals Leuven. Studies were performed using a 3.2 mm diameter solid state manometric and impedance catheter incorporating twenty five 1 cm-spaced pressure sensors and twelve 2 cm long impedance segments (Unisensor USA Inc, Portsmouth, N.H.). Subjects were intubated with topical anaesthesia (lignocaine gel) used to reduce discomfort and the catheter was

positioned with sensors straddling the entire pharyngo-esophageal segment (velo-pharynx to proximal esophagus). Pressure and impedance data were acquired (upright position) at 20 Hz (Solar GI acquisition system, MMS, The Netherlands). As per routine clinical fluoroscopy, test boluses of 1-10 ml liquid (dependent on age and tolerance) were administered orally via syringe. All bolus stock contained 1% NaCl to improve bolus conductivity. Video-loops of the fluoroscopy images of swallows were simultaneously acquired (25 frames/sec). The first swallow that followed bolus administration to the mouth was defined as the first swallow. If the first swallow failed to clear the bolus from the oral cavity, tongue-base, valleculae and/or piriform sinus, and the patient swallowed again whilst being screened, then these subsequent swallows were also analyzed and defined as clearing swallows.

[0222] Fluoroscopic assessment of aspiration/penetration, data analysis, pharyngeal pressure-flow variables, UES relaxation variables and statistical analysis were conducted according to Example 1.

[0223] Results

[0224] Twenty nine first swallows were evaluated with the three modalities of fluoroscopy, manometry and impedance. Of these, 15 swallows (in 8 patients) failed to clear the bolus fully and in these patients a further 38 clearing swallows were recorded. Bolus volumes administered to the mouth varied from 1-10 ml (mean 2.2 ± 2 ml). Mostly boluses administered were of 1 ml (19 of 29 first swallows). The potential confounding effects of first swallow volume were investigated by Mann-Whitney Rank Sum Test (of 1 ml vs. volumes >1 ml), Kruskal-Wallis ANOVA on ranks and Spearman Rank Order Correlation. No direct comparison of any variable with administered volume achieved statistical significance. Swallow variables for first and clearing swallows were only different for UES-RI (Table 2) and therefore data for first and clearing swallows were grouped for the purposes of comparison between swallows with and without aspiration and bolus residue.

TABLE 2

	All First Swallows	All Clearing Swallows (p-value vs. FIRST SWs)	Swallows WITHOUT Aspiration	Swallows WITH Aspiration (p-value vs. NO Asp)
No. Swallows Analyzed	29	38	51	16
PeakP	193	167 (0.296)	190	106 (0.058)
mmHg	[131, 207]	[103, 211]	[128, 210]	[94, 208]
PNadImp	28	23 (0.224)	24	30 (0.236)
mmHg	[18, 59]	[14, 34]	[14, 39]	[19, 46]
Flow Interval	625	783 (0.737)	550	1342 (0.003)
msec	[412, 1291]	[403, 1332]	[375, 1043]	[644, 1876]
TNadImp-PeakP	299	287 (0.467)	299	269 (0.542)
msec	[216, 339]	[197, 326]	[211, 332]	[207, 337]
Swallow Risk Index	11	10 (0.945)	6	22 (0.001)
SRI	[4, 22]	[4, 25]	[3, 16]	[16, 41]
UES Relaxation	429	583 (0.022)	471	611 (0.192)
Interval msec	[313, 607]	[394, 825]	[350, 703]	[392, 877]
UES Intrabolus	21	25 (0.466)	23	24 (0.659)
Pressure mmHg	[15, 28]	[12, 34]	[13, 33]	[18, 30]
Nadir UES	15	16 (0.894)	16	14 (0.780)
Pressure mmHg	[10, 18]	[10, 19]	[11, 19]	[10, 18]
UES resistance	55	40 (0.296)	46	38 (0.358)
mmHg/sec	[30, 72]	[31, 58]	[31, 70]	[31, 54]

Summary data of 67 bolus swallows in patients showing the relationships among important objective variables (pharyngeal variables shaded) and the presence of aspiration-penetration. Data presented as median [IQR]. P-values of Mann-Whitney Rank Sum Test for control vs. patient and no aspiration vs. aspiration shown in parentheses. Data for which $p < 0.05$ are highlighted in bold text.

[0225] Changes in Swallow Variables in Relation to Fluoroscopy Findings

[0226] Aspiration-penetration was observed during a total of 16 swallows comprising 8 first and 8 clearing (in 8 patients). The median [IQR] aspiration score was 8 [5, 8] for these aspiration-associated swallows. Patient swallows with aspiration-penetration had a longer flow interval and higher SRI than those without aspiration (Table 2) and, on a swallow by swallow basis, the presence of aspiration-penetration was significantly related to a longer flow interval (OR 4.2 [1.6, 11.1], $p < 0.001$) and higher SRI (OR 23.4 [1.4, 391], $p < 0.05$). A trend for lower peak pressure was also apparent ($p = 0.058$, Table 2).

[0227] Both longer flow interval and higher SRI correlated with higher aspiration scores (Spearman Rank Order Correlations of $r = 0.336$, $p = 0.006$ and $r = 0.381$, $p = 0.002$ respectively). All other swallow variables were not significantly different in relation to the presence/absence of aspiration (Table 2). Example tracings and calculations from a patient with deglutitive aspiration are provided in FIG. 10 (A-F).

[0228] Patient swallows with bolus residue compared to those without residue had lower peak pressure (100 [88, 113] vs. 194 [164, 212] mmHg, $p < 0.001$), a longer flow interval (1290 [580, 2300] vs. 1177 [704, 1668] msec, $p = 0.006$) respectively, $p = 0.008$), a longer UES-RI (625 [534, 921] vs. 450 [313, 0.611] msec, $p = 0.007$) and higher UES-IBP 30 [24, 37] vs. 20 [11, 27] mmHg, $p = 0.001$). Other swallow variables were not significantly different in relation to the presence/absence of residue. The presence of bolus residue following clearance failure was not related to aspiration score (odds ratio 1.1 [0.9, 1.3], $p = 0.339$).

[0229] Predictive Value of Swallow Risk Index for Detecting Aspiration

[0230] We assessed whether the average SRI recorded in an individual patient could predict the presence/absence of aspiration during fluoroscopy of the same patient. The average SRI correlated strongly with the average aspiration score (Spearman Rank Order Correlation of 0.753, $p = 0.006$). Based on kappa values, an average SRI of 15 was the optimal threshold for accurate prediction of aspiration in the patient cohort (kappa 0.82) (FIG. 11A) and was also optimal in terms of sensitivity (1.0) and specificity (0.83) (FIG. 11B).

[0231] Discussion

[0232] The present study has again established that combined manometry and impedance measurements can detect alterations in pressure-flow characteristics of pharyngeal swallow that predispose to aspiration risk, this time in pediatric patients with suspected aspiration and high dysphagia.

[0233] Whilst it has been widely demonstrated that volume swallowed can influence individual functional parameters, in the current study these volume effects appeared small and there was no significant volume effect on the SRI. This further demonstrates the added value of combining variables to derive the SRI. This is particularly encouraging of utility in pediatric patients, in whom the volume administered during swallow testing is very difficult to control and, even if a standardised volume is administered to the mouth, it may nevertheless take several swallows to consume. The fact that the predictive value of the SRI appears to be robust in the face of the potential confounding factors such as age and control of bolus volume is supportive of this new methodology having very real clinical potential as a screening tool for aspiration risk in the pediatric population.

Example 3

Assessment of Pharyngeal Motor Function Relevant to Post-Swallow Bolus Residue

[0234] The aim of this study was to apply the approach developed in Example 1, i.e. the use of high resolution intraluminal manometry combined with impedance measurement, for the objective assessment of pharyngeal function relevant to post-swallow bolus residue. This approach was evaluated to determine if it enables recognition of subjects with swallowing dysfunction causing bolus residue, without performance of fluoroscopy.

[0235] Methods

Subjects

[0236] 23 dysphagic patients (17 adults, 6 children, 14 males, mean age 55 years, age range 2-95 years) were referred to the pediatric and adult swallowing clinics for a videomanometry study of the pharynx and esophagus. Underlying diseases/conditions were identified through a review of medical records. Sixteen patients had a neurological history comprising 7 adults with stroke, 4 children with cerebral palsy, 2 adults with Parkinson's disease, 2 adults with dementia and 1 adult post neurosurgery. Of the remainder of patients, 1 adult was post cervical surgery, 1 child had cardiovascular disease, 2 adults had a motility disorder and 2 adults and 1 child had unknown etiologies at the time of study. For comparison, ten healthy adult subjects were recruited who had no swallowing difficulties, nor other symptoms suggestive of a motility disorder (5 male, mean 36.6 years, range 24-47 years). The study protocol was approved by the Research Ethics Committee, University Hospitals Leuven, Belgium.

[0237] Measurement Technique

[0238] All fluoroscopy studies were performed in the Radiology Department, University Hospitals Leuven. Studies were performed using a 3.2 mm diameter solid state manometric and impedance catheter incorporating twenty five 1 cm-spaced pressure sensors and twelve 2 cm long impedance segments (Unisensor USA Inc). Subjects were intubated (topical anaesthesia—Lignocaine) and the catheter was positioned with sensors straddling the entire pharyngo-esophageal segment (velo-pharynx to proximal esophagus). Pressure and impedance data were acquired (upright position) at 20 Hz (Solar GI acquisition system, MMS, The Netherlands). Semi-solid test boluses were administered orally via syringe. All bolus stock contained 1% NaCl to enhance conductivity. As per routine clinical fluoroscopy, test boluses to patients were of 1-15 ml semi-solid. For controls, 2x10 ml semi-solid boluses were administered, both of which were recorded during fluoroscopy. Video-loops of the fluoroscopy images of swallows were simultaneously acquired (25 frames/sec). The first swallow that followed bolus administration to the mouth was defined as the first swallow. If the first swallow failed to clear the bolus from the oral cavity, tongue-base, valleculae and/or piriform sinus, and the subject/control was asked to swallow again whilst being screened, these subsequent swallows were also analyzed and defined as clearing swallows.

[0239] Fluoroscopic Assessment of Bolus Residue and Aspiration-Penetration

[0240] Fluoroscopic images from patient and control studies were scored for residue and the occurrence of aspiration-penetration blind to the impedance findings. Swallows were also assessed for the presence or absence of post-swallow residue in the valleculae, piriform sinus and/or posterior pharyngeal wall and also scored from 1-6 according to the number of structures showing evidence of residue: No residue in

any of these structures was assigned a score of 1. If residue was present, then additional scores were weighted towards the anatomical regions in which residue posed an aspiration risk (+1 for valleculae, +2 for piriform sinus and +2 for posterior pharyngeal wall). Hence valleculae only=2, posterior pharyngeal wall or piriform sinus only=3, valleculae and posterior pharyngeal wall or piriform sinus=4, posterior pharyngeal wall and piriform sinus=5; all structures=6. Swallows were assessed for the presence of aspiration-penetration using a validated 8-point score (Rosenbek J C, supra), influenced primarily by the depth to which material passes in the airway and by whether or not material entering the airway is expelled during the swallow sequence (Score 1=no aspiration, 2-5=penetration, 6-8=aspiration).

[0241] Data analysis, pharyngeal pressure-flow variables, UES relaxation variables and statistical analysis were conducted according to Example 1. However, in this study, we evaluated the SRI in relation to bolus residue.

[0242] Results

[0243] Seventy six swallows were recorded in patients with the three modalities of manometry, impedance and fluoroscopy. Swallows comprised 37 first swallows, of which 24 failed to clear, and a further 39 clearing swallows. Thirty nine

swallows were recorded in controls with all modalities comprising 18 first swallows and a further 21 clearing swallows.

[0244] Patient vs. Control Swallows

[0245] There was little scope to standardise bolus volume administered to patients, nevertheless there were no significant differences amongst first swallow variables recorded following administration of different bolus volumes. Comparisons amongst the different swallow variables calculated for semisolid boluses in patients and controls are shown in Tables 3 and 4.

[0246] For pharyngeal variables (Table 3) patient swallows, compared to control, had lower PeakP, lower PNadImp, shorter TNadImp-PeakP (trend $p=0.053$), longer Flow Interval and a higher SRI. For UES variables (Table 4) patient swallows, compared to control, had a longer UES-RI, lower UES-IBP and lower UES resistance. The swallow risk index was elevated in patients compared to controls (Table 3).

[0247] In patients, 46% of swallows had residue compared to 31% of control swallows. Qualitatively, the amount of residue was also less in controls, however, as the scoring system employed only assessed residue based on its presence and the number of structures involved, this difference was not apparent within the quantitative score (median residue score of 3 [2, 5] vs. 3 [2, 4] for swallows with residue in patients and controls respectively).

TABLE 3

		CONTROLS			PATIENTS		
		All Swallows	WITHOUT Residue	WITH Residue (p vs. NO Residue)	All Swallows (p vs. Control)	WITHOUT Residue	WITH Residue (p vs. NO Residue)
No. Sw Total (first/clearing)		39 (18/21c)	27 (11/16c)	12 (7/5c)	76 (37/39c)	41 (20/21c)	35 (17/18c)
PeakP mmHg	First Sw	147 [188, 205]	145 [118, 178]	190 [102, 234]	110 (0.067) [89, 186]	124 [91, 183]	109 [64, 188]
	Clearing Sw	212 [131, 263]	222 [130, 268]	195 [157, 250]	188 (<0.001) [71, 197]	182 [104, 216]	71 (0.002) [44, 137]
	All Sw	178 [128, 234]	150 [130, 245]	193 [125, 233]	113 (<0.001) [72, 190]	144 [100, 212]	101 (0.008) [61, 160]
PNadImp mmHg	First Sw	29 [19, 38]	24 [10, 31]	36 (0.046) [32, 38]	14 (0.048) [4, 33]	9 [4, 24]	22 [7, 41]
	Clearing Sw	26 [18, 41]	26 [13, 38]	40 (0.127) [25, 74]	26 [17, 42]	32 [14, 70]	25 [17, 31]
	All Sw	27 [19, 40]	25 [12, 34]	37 (0.014) [31, 48]	22 [9, 40]	18 [6, 60]	25 [15, 33]
TNadImp-PeakP mmHg	First Sw	363 [248, 415]	369 [297, 421]	321 [208, 415]	306 (0.062) [160, 366]	349 [200, 391]	229 (0.028) [126, 324]
	Clearing Sw	243 [172, 323]	245 [149, 328]	233 [192, 326]	205 [123, 264]	234 [170, 280]	149 (0.037) [111, 218]
	All Sw	280 [180, 381]	297 [163, 396]	264 [205, 379]	224 (0.058) [146, 321]	263 [187, 356]	203 (0.009) [114, 276]
Flow Interval msec	First Sw	313 [250, 591]	278 [225, 325]	591 [250, 1319]	736 (0.081) [281, 1110]	500 [225, 802]	1028 (0.012) [523, 1606]
	Clearing Sw	425 [188, 765]	430 [175, 651]	402 [188, 956]	794 (0.05) [300, 1378]	512 [244, 1317]	812 [420, 2182]
	All Sw	325 [225, 680]	325 [225, 550]	497 [213, 1037]	789 (0.005) [306, 1280]	525 [242, 1167]	994 (0.020) [425, 1784]
Swallow Risk Index	First Sw	4.2 [2.0, 10.7]	2.3 [1.5, 7.0]	11.4 (0.037) [4.4, 24.6]	6.8 [1.7, 17.1]	2.3 [1.0, 8.5]	12.0 (0.009) [3.9, 32.5]
	Clearing Sw	7.0 [1.7, 10.6]	3.5 [1.5, 10.1]	10.2 [4.4, 15.0]	15.5 (0.006) [3.7, 42.6]	7.9 [2.5, 40.6]	27.6 (0.060) [8.7, 52.4]
	All Sw	4.4 [1.9, 10.7]	2.8 [1.5, 8.2]	10.2 (0.025) [5.0, 19.1]	8.7 (0.018) [2.6, 33.7]	3.9 [1.3, 27.8]	15.4 (0.004) [7.7, 38.5]

Summary data of 115 swallows in controls and patients showing the relationships among important objective pharyngeal variables and the presence of post-swallow residue.

Data presented as median [IQR].

Mann-Whitney Rank Sum Test P-values < 0.1 for control vs. patient and residue vs. no residue are shown in parentheses.

Data for which $p < 0.05$ are shaded grey for control vs. patient and shaded black for no-residue vs. residue.

TABLE 4

		CONTROLS			PATIENTS		
		All Swallows	WITHOUT Residue	WITH Residue (p vs. NO Residue)	All Swallows (p vs. Control)	WITHOUT Residue	WITH Residue (p vs. NO Residue)
No. Sw Total (first/clearing)		39 (18f/21c)	21 (11f/16c)	12 (7f/5c)	76 (37f/39c)	41 (20f/21c)	35 (17f/18c)
UES Relaxation Interval msec	First Sw	422 [349, 597]	425 [333, 576]	402 [359, 775]	786 (0.001) [523, 1174]	644 [381, 938]	921 (0.093) [561, 1201]
	Clearing Sw	350 [288, 475]	350 [302, 487]	349 [213, 532]	670 (<0.001) [463, 1136]	489 [2.94, 721]	1136 (<0.001) [784, 1460]
	All Sw	402 [325, 513]	403 [325, 513]	390 [275, 589]	710 (<0.001) [484, 1144]	540 [325, 884]	1021 (<0.001) [638, 1224]
UES Intrabolus Pressure mmHg	First Sw	30 [20, 48]	24 [20, 48]	35 [16, 55]	16 (0.002) [8, 24]	18 [11, 27]	15 [7, 22]
	Clearing Sw	7 [4, 37]	6 [3, 22]	37 [10, 42]	17 [12, 24]	17 [12, 24]	16 [8, 28]
	All Sw	21 [7, 38]	20 [6, 35]	36 (0.053) [6, 45]	16 [8, 24]	17 [12, 24]	15 [7, 24]
Nadir UES Pressure mmHg	First Sw	15 [3, 33]	4 [0, 33]	15 [3, 36]	5 [0, 12]	10 [2, 16]	2 (0.072) [0, 10]
	Clearing Sw	2 [-1, 20]	2 [-1, 5]	31 (0.056) [2, 38]	9 [1, 16]	13 [2, 16]	9 [-2, 13]
	All Sw	4 [0, 25]	3 [-1, 16]	18 (0.035) [4, 36]	8 [0, 15]	12 [2, 16]	3 (0.023) [0, 11]
UES resistance mmHg/sec	First Sw	52 [29, 98]	48 [29, 77]	57 [39, 157]	25 (<0.001) [12, 31]	29 [22, 44]	18 (0.035) [10, 29]
	Clearing Sw	17 [12, 103]	15 [10, 54]	106 (0.091) [18, 204]	22 [10, 52]	36 [19, 64]	16 (0.005) [6, 22]
	All Sw	42 [16, 100]	30 [14, 59]	77 (0.051) [26, 169]	22 (0.004) [12, 38]	30 [19, 53]	16 (<0.001) [6, 25]

Summary data of 115 swallows in controls and patients showing the relationships among important objective UES variables and the presence of post-swallow residue.

Data presented as median [IQR].

Mann-Whitney Rank Sum Test P-values < 0.1 for control vs. patient and residue vs. no residue are shown in parentheses.

Data for which $p < 0.05$ are shaded grey for control vs. patient and shaded black for no-residue vs. residue.

[0248] Several variables were different in relation to the presence of post-swallow residue and there were clear differences between patients and controls in terms of the specific variables altered. PeakP, for example, was significantly lower during patient swallows with residue compared to those without residue; however PeakP did not differ in this way in controls (Table 3). Patient swallows with residue had significantly shorter TNadImp-PeakP, longer Flow Interval, longer UES-RI and lower UES resistance; none of these variables were significantly different in control swallows with residue (Tables 3 and 4). Conversely, control swallows with residue had an elevated PNadImp, which was not the case with patient swallows with residue (Table 3). Finally, control swallows with residue had a significantly higher Nadir UESP and UES resistance while patient swallows with residue conversely had a significantly lower Nadir UESP and UES resistance (Table 4). In contrast to all individual variables, the swallow risk index was significantly higher in relation to residue for swallows in both patients and controls (Table 3).

[0249] Variables were similarly altered in relation to bolus residue score. In patients, higher bolus residue score correlated with lower PeakP ($r=-0.285$, $p=0.013$), shorter TNadImp-PeakP ($r=-0.313$, $p=0.006$), longer Flow Interval ($r=0.242$, $p=0.035$) and longer UES-RI ($r=0.428$, $p=0.0001$), while similar relationships were not observed in controls. In controls, higher bolus residue score correlated with higher PNadImp ($r=0.381$, $p=0.017$), higher UES-IBP ($r=0.328$, $p=0.042$) and higher Nadir UESP ($r=0.351$, $p=0.028$), while

similar relationships were not observed in patients. Residue score correlated with lower UES resistance ($r=-0.324$, $p=0.004$) in patients but inversely higher UES resistance ($r=0.341$, $p=0.034$) in controls. A higher residue score correlated with higher SRI in both patients ($r=0.329$, $p=0.004$) and controls ($r=0.333$, $p=0.0387$). FIG. 12 shows the relationship between the extent of residue and the median SRI in patients and controls.

[0250] As the SRI was the only variable significantly elevated in relation to residue in both patients and controls, we assessed the predictive value of SRI for detecting residue. Receiver operator curves showing the sensitivity and specificity of SRI are shown in FIG. 13, this shows that the predictive value of the SRI for detection of residue can be improved by averaging the findings over several swallows. An average SRI cut-off of 9 appears to be optimal for detecting residue with an overall sensitivity of 75% and specificity of 80% (81%/71% in patients only and 80%/75% in controls only).

[0251] Patient Swallows with Aspiration-Penetration

[0252] Six aspiration-penetration episodes were recorded on fluoroscopy in 4 patients (3 penetration/3 aspiration; average aspiration-penetration score 4.8, range 2-8; average residue score 5.2, range 2-6). Of these, two episodes occurred during first swallows and four during clearing swallows. Despite low numbers of analysable events, swallows with aspiration compared to those without, had a lower PeakP (55 [30, 100] vs. 120 [81, 193] mmHg respectively, $p=0.005$) and

a longer UES-RI (1179 [857, 1474] vs. 644 [741, 1029] msec, $p=0.018$) and there was also a clear statistical trend in favour of a shorter TNadImp-PeakP (160 [-11, 246] vs. 227 [149, 333] msec, $p=0.073$) and a higher SRI (22.3 [13.1, 61.8] vs. 8.3 [2.5, 33.4], $p=0.075$).

[0253] Discussion

[0254] A novel automated approach to the analysis of pharyngeal manometry and impedance recordings was used to characterise pharyngeal function in relation to ineffective deglutition leading to bolus residue. While, bolus residue was evident on both patients with dysphagia as well as asymptomatic controls, the specific functional variables related to the presence of residue differed between patients and controls. In contrast, a swallow risk index, which was based upon the objective calculation of four pharyngeal pressure-flow variables, was elevated in relation to residue in both patients and controls.

[0255] Our prior studies have concentrated on optimising criteria for the direct detection of bolus residue using intraluminal impedance. However, we discovered large differences in the optimal criteria determined for controls and patients as well as large inter-patient differences related to pathology. Our new approach combines pressure and impedance measurement to derive a range of new swallow function variables which can be combined in a manner that predicts whether swallows are likely to be ineffective based on the SRI. This contrasts with the standard approach which evaluates impedance and pressure findings separately. As we clearly show, pharyngeal UES motor function does not always empty the pharynx in healthy controls, and our new approach is therefore markedly superior, having high predictive value in both controls as well as patients.

[0256] Many swallows in both patients and controls were observed to be ineffective and failed to completely clear the bolus. We were surprised to discover that residue was scored similarly for patients and controls, even though, qualitatively, controls exhibited only trace amounts of residue coating structures, whilst in patients residue tended to be of greater volume. The fact that the impedance-based Flow Interval, was significantly longer in relation to residue, in patients only and not controls, provides some evidence for the volume of residue being larger in patients. This aspect of bolus quantity was not assessed in the derivation of the residue score because it was considered too subjective. This highlights one of the major limitations of fluoroscopy-based scoring systems. The aspiration-penetration score for example, has been found to have a high degree of inter/intra-rater reliability, however even this widely utilized system is limited by the fact that it does not distinguish volume aspirated and therefore trace vs. large volume aspiration below the vocal cords is scored equally.

[0257] Although residue scores were similar the functional variables found to be altered in relation to residue were very different in controls vs. patients. In controls, residue was mostly related to variables suggestive of increased UES resistance due to impaired UES relaxation, i.e. increased PNadImp (suggestive of increased pharyngeal intrabolus pressure), increased UES-IBP, increased Nadir UESP and increased UES resistance. In contrast, residue in patients was mostly related to poor bolus propulsion and pharyngeal/UES weakness, i.e. short TNadImp-PeakP, low pharyngeal PeakP, prolonged UES-RI, low nadir UESP and low UES resistance. These findings in our patients are perhaps not surprising given that the majority had a neurological basis for their dysphagia.

[0258] Despite these large differences in controls compared to patients with respect to the specific functional variables governing pharyngeal effectiveness, the swallow risk index was nevertheless elevated in relation to residue and was highly predictive of residue for both controls and patients. This clearly demonstrates the inherent value of taking into account several different measures of function, which in turn delivers a more accurate global assessment of pharyngeal effectiveness. In practise, having utilized a global measure such as the SRI to establish pharyngeal effectiveness, one could then turn to individual functional variables to identify pathophysiological causes. This potentially allows for a relatively specific diagnosis of varying mechanical dysfunctions. From such analysis, it may be possible to devise well targeted therapeutic interventions and, in turn, track the effectiveness of such interventions.

[0259] The fact that the predictive value of the SRI, in relation to residue, appeared to be similar for patients and controls and robust in the face of the potential confounding factors, such as age, engenders confidence that this methodology has very real potential for clinical implementation

Example 4

Identification of Pressure-Flow Variables as Markers of Susceptibility for Development of Post-Operative Dysphagia

[0260] The aim of this experiment was to determine if the methods of the present invention could be used for an objective assessment of esophageal function in order to predict post-operative dysphagia following Nissan Fundoplication surgery.

[0261] Esophageal dysphagia, the failure of food boluses to clear from the esophageal lumen, is a post-operative complication of anti-reflux surgery for gastroesophageal reflux disease (GERD). The genesis of this problem lies in fact that anti-reflux operation (e.g. Nissan Fundoplication) causes a restriction at the esophago-gastric junction, which, while beneficial for reducing gastroesophageal reflux from the stomach into the esophagus, may also interrupt normal antegrade flow from the esophageal lumen into the stomach during swallowing. Whilst dysphagia is a common symptom of GERD which often resolves following surgery, approximately 1 in 3 patients develop dysphagia as a consequence of surgery. It would be very useful to determine which patients are susceptible to developing post-operative complications of dysphagia; however, there are no tests presently that can be performed pre-operatively which will predict the likelihood of dysphagia due to surgery.

[0262] There have been several studies that have evaluated intraluminal manometry of the esophagus and esophago-gastric junction to determine if pressure variables (lower esophageal sphincter pressure and peristaltic pressures) can predict post-operative dysphagia. These studies have not been able to identify a measurable parameter predictive of dysphagia. Intraluminal impedance has also been used to define bolus transit and clearance in patients and this method similarly fails to predict post-operative dysphagia.

[0263] This important clinical question has been addressed using the novel analysis method of the present invention which combines pressure and impedance measurements to produce novel esophageal pressure-flow variables guided predominately by the timing of the impedance nadir recorded during bolus flow. The aim of this study was to determine if

one or more of these variables was a marker of susceptibility for development of post-operative dysphagia.

[0264] Methods

[0265] Manometry and impedance recordings from 18 adult GERD patients (8 female/10 male, aged from 31-70 years) who received Nissen Fundoplication surgery were analyzed. All patients underwent esophageal manometry using a 9 channel perfusion manometry catheter incorporating 4 impedance segments 5 cm apart. The configuration of the catheter is shown in FIG. 14A. Studies were performed both before and after surgery in the Department of Surgery, University of Adelaide. Subjects were intubated and the catheter was positioned to record esophageal and esophago-gastric junction pressures. Ten x 10 ml viscous boluses were administered orally via syringe and the resulting motility recorded.

[0266] Assessment of Dysphagia Symptoms

[0267] Evidence of symptoms of dysphagia was obtained at the time of study. The dysphagia score of Dakkak and Bennett, 1992, *J. Clin. Gastroenterol.* 14: 99-100 was used. This assesses dysphagia severity based on ability to swallow nine items of food. A score of 1 or more out of 45 is indicative of the presence of Dysphagia symptoms.

[0268] Data Analysis

[0269] Raw manometric and impedance data for each bolus swallow were visualised over 30 second windows and exported from the recording system in ASCII text format and then analyzed by a separate computer using MATLAB (version 7.9.0.529; The MathWorks Inc). Pressure and impedance data were smoothed by a cubic interpolation method which doubled the temporal data and increased the amount of spatial data by a factor of 10, hence achieving a virtual increase from 1 value per 5 cm sampled at 30 Hz to 10 values per cm sampled at 60 Hz. The raw impedance data were standardised to the median impedance (presented therefore as median standardised units (msu) rather than ohms).

[0270] Derivation of Esophageal Pressure-Flow Variables

[0271] The spatial region of the esophageal pressure wave recorded across the 4 pressure sensor and impedance segment array was analyzed in a separate pressure-impedance plot (FIG. 14B). The timings of the esophageal impedance nadir (NadImp) and Peak Pressure (PeakP) and the time interval from NadImp to Peak Pressure (TNadImp-PeakP) were automatically determined at all positions along the plot (FIG. 14B).

[0272] Having identified NadImp and PeakP at all positions, the rate of progression of NadImp (NadImp rate) and Peak Pressure (PeakP rate) were calculated. Guided by the timing of NadImp, the following variables were also determined at each position and averaged for both the entire pressure-impedance array and for the distal half only of the pressure-impedance array:

[0273] The pressure at the time of NadImp (PNadImp) (FIG. 14C).

[0274] Pressure of PeakP (FIG. 14C).

[0275] The median intrabolus Pressure (mIBP); estimated by calculating the median pressure recorded from NadImp to the mid time point of TNadImp-PeakP (FIG. 14D).

[0276] The IBP slope, defined by the change in pressure over time from PNadImp to the pressure at the mid time point of TNadImp-PeakP.

[0277] All esophageal pressures during swallowing were reference to baseline pre-swallow esophageal pressures.

[0278] Derivation of Esophago-Gastric Junction Relaxation Pressures

[0279] Esophago-gastric junction (EGJ) relaxation characteristics were measured using the established method of Kahrilas P J et al., 2008, *J. Clin. Gastroenterol.* 42: 627-635. The cumulative duration of EGJ relaxation was plotted from the minimum to the maximum pressure recorded in the EGJ. This plot was used to calculate 4 second integrated relaxation pressure. Resting EGJ pressure was recorded for 10 seconds prior to EGJ relaxation onset. All EGJ pressures were referenced to average gastric pressure.

[0280] Statistics

[0281] Non-parametric grouped data were presented as medians [inter-quartile range] and compared using the Mann-Whitney Rank Sum Test. Parametric grouped data were presented as means $\pm$ SEM and compared using a t-test. Paired data pre/post-surgery were compared using Wilcoxon Signed Rank Test or paired t-Test. For multiple comparisons Kruskal-Wallis One Way Analysis of Variance on Ranks or One Way Analysis of Variance was used and pair-wise comparisons were made using multiple comparison procedures (Dunn's Method or Holm-Sidak method). For all tests a $p < 0.05$ indicated statistical significance.

[0282] The sensitivities and specificities were determined for candidate predictive variables. The optimal level of concordance between baseline criteria and the presence of post-operative dysphagia was expressed with Cohen's kappa Statistic. The scale for kappa values is: 0.00=no agreement, 0.00-0.2=slight, 0.21-0.40=fair 0.41-0.60=moderate, 0.61-0.8=substantial, 0.81-1.00=almost perfect.

[0283] Results

[0284] Eight patients reported dysphagia symptoms before surgery, compared to fourteen after surgery. In no patients with pre-operative dysphagia, did the symptoms completely resolve post-operatively. However, six patients without dysphagia symptoms developed "new" dysphagia post-operatively. Only four patients reported no dysphagia symptoms both pre and post-surgery.

[0285] The Dakkak dysphagia score was not significantly different following surgery (average score 6 ± 2 pre vs. 9 ± 2 post, $p=0.327$). Pre-surgical dysphagia scores were significantly higher in patients with a hiatus hernia (HH) compared to no HH (median score 10 [0-21] vs. 0 [0, 3], $p=0.032$). Increased hernia size was also related to higher pre-operative dysphagia scores (Spearman Rank Order Correlation $r=0.562$, $p=0.015$). Baseline esophageal and EGJ variables were however not significantly different in relation to HH.

[0286] Seven patients received a partial wrap Nissen and 11 a full wrap Nissen. Post-surgical dysphagia scores were not significantly different in relation to operation type (median score 6 [0-21] partial vs. 4 [0-12] full Nissen, $p=0.466$). Post-operative esophageal and EGJ variables were not significantly different in relation to operation type. Table 5 shows results for all measured pressure-flow variables for all patients before and after surgery. Esophageal variables were not significantly altered by surgery, whilst EGJ variables were all significantly altered consistent with fundoplication increasing pressures at the level of the EGJ (Table 5).

[0287] Table 5 also shows results for variables grouped based on the time of measurement (before/after surgery) and the presence of dysphagia symptoms before or after surgery. Across pre-surgical studies, patients with dysphagia symptoms pre-surgery had lower Peak Pressures than those without symptoms (29 vs. 45 mmHg, $p < 0.05$).

TABLE 5

Variable	All-Patients		Results Before Surgery vs. Dysphagia Before Surgery		Results Before Surgery vs. Dysphagia After Surgery		Results After Surgery vs. Dysphagia After Surgery	
	Pre-Op	Post-Op	No Dysphagia	Dysphagia Sx	No Dysphagia	Dysphagia Sx	No Dysphagia	Dysphagia Sx
Esophageal Peak P mmHg	48 ± 3	49 ± 4	50 ± 3	45 ± 6	45 ± 3	48 ± 4	68 ± 5	44 ± 4
Distal Peak P mmHg	44 ± 4	56 (0.069) ± 6	45 [40, 61]	29 (0.037) [23, 48]	43 ± 4	44 ± 5	74 ± 17	50 ± 6
PNadImp mmHg	12 [7, 22]	12 [12, 16]	12 ± 2	16 ± 3	10 ± 2	15 ± 2	6 [3, 11]	15 (0.080) [8, 17]
Distal PNadImp mmHg	5 [4, 9]	9 [3, 23]	6 [4, 12]	4 [4, 8]	5 [-1, 6]	5 [4, 12]	5 ± 2	15 ± 4
IBP mmHg	17 ± 2	17 ± 2	15 ± 3	19 ± 3	10 ± 2	19 (0.042) ± 2	10 ± 2	18 ± 3
Distal IBP mmHg	10 ± 2	16 ± 3	10 ± 3	10 ± 3	3 [-2, 7]	8 (0.100) [5, 16]	9 ± 2	18 ± 4
IBP Slope mmHg/sec	9 ± 2	9 ± 2	7 [5, 10]	4 [3, 23]	5 [0, 7]	7 [4, 18]	9 [5, 18]	7 [3, 13]
Distal IBP Slope mmHg/sec	7 ± 1	10 ± 2	7 ± 2	8 ± 2	2 ± 1	9 (0.047) ± 2	8 ± 2	10 ± 2
TNadImp-PeakP sec	2.0 ± 0.2	1.8 ± 0.3	2.1 ± 0.3	1.9 ± 0.4	2.7 ± 0.2	1.8 (0.082) ± 0.2	2.6 ± 0.7	1.6 (0.091) ± 0.2
Dist. TNadImp-PeakP sec	2.8 ± 0.3	2.4 ± 0.3	2.9 ± 0.4	2.7 ± 0.4	4.0 ± 0.3	2.5 (0.020) ± 0.3	3.2 ± 0.7	2.1 ± 0.3
Dysphagia Risk Index	23 [14, 95]	33 [2, 325]	22 [11, 172]	40 [16, 97]	9 [-2, 19]	43 (0.017) [20, 177]	33 [8, 61]	32 [2, 379]
EGJ	Pre-Op	Post-Op	No Dysphagia Pre-Op	Dysphagia Pre-Op	No Dysphagia Post-Op	Dysphagia Post-Op	No Dysphagia	Dysphagia
Basal EGJ pressue mmHg	7 [4, 12]	18 (0.017) [8, 23]	6 [3, 10]	8 [6, 15]	6 [2, 10]	7 [2, 10]	18 [8, 29]	15 [8, 24]
Nadir EGJ pressue mmHg	-2 [-4, 0]	2 (0.016) [-2, 10]	-3 ± 1	-1 ± 1	-2 ± 2	-2 ± 1	3 [-2, 8]	2 [-2, 11]
4 sec IRP mmHg	0 [-2, 3]	6 (0.008) [-1, 14]	-1 ± 1	1 ± 1	-1 ± 2	1 ± 1	6 [0, 11]	6 [0, 15]

Pressure flow variables for viscous swallows pre and post-surgery and in relation to the presence of dysphagia pre and/or post-surgery.

Paired data from all patients before and after surgery compared using Wilcoxon Signed Rank Test or paired t-test.

Data for patients with and without dysphagia compared using Mann-Whitney Rank Sum Test or t-test.

P-values 50.10 shown in parenthesis.

Significant comparisons highlighted as black cells.

[0288] No other variable was significantly altered in relation to dysphagia pre-surgery. Across post-surgical studies, no variable was significantly altered in relation to dysphagia post-surgery (Table 5). When variables recorded pre-surgery were compared for patients with and without dysphagia symptoms post-surgery several variables were significantly different (Table 5). At baseline study, patients who developed dysphagia symptoms post-surgery had elevated esophageal IBP (also referred to as distal IBP) (19 vs. 10 mmHg, $p < 0.05$), elevated esophageal IBP slope (also referred to as distal IBP Slope) (9 vs. 2 mmHg/sec, $p < 0.05$) and shorter esophageal TNadImp-PeakP (also referred to as distal TNadImp-PeakP) (2.5 vs. 4.0 sec, $p < 0.05$). Based on these findings a dysphagia risk index (DRI) was defined by the formula:

$$DRI = IBP \times IBP \text{ Slope} \times TNadImp\text{-}PeakP^{-1}$$

[0289] At baseline study, patients who developed dysphagia symptoms post-surgery had an elevated DRI (43 vs. 9, $p < 0.05$). Table 6 compares patients with no dysphagia symptoms with those who had symptoms pre and post-surgery and

those that had symptoms after surgery only. Preoperative measurements of esophageal TNadImp-PeakP and DRI were significantly different among the three groups using ANOVA. Pairwise comparisons of esophageal TNadImp-PeakP and DRI were also significantly different between patients with no dysphagia symptoms and those with symptoms after surgery only (Table 6). In contrast, post-operative measurements of these variables were not significantly different between the three groups of patients (Table 6).

[0290] The predictive value of baseline esophageal TNadImp-PeakP, esophageal IBP Slope, IBP and Dysphagia Risk Index for determining post-operative dysphagia symptoms was assessed. Optimal predictive criteria were an esophageal TNadImp-PeakP of < 3.5 sec (sens 0.75, spec 0.86, Kappa 0.557), esophageal IBP Slope > 5 (sens 0.71, spec 1.0, Kappa 0.526) and IBP > 12 (sens 0.75, spec 0.79, Kappa 0.454). Optimal criteria for the Dysphagia Risk Index was > 14 (sens 0.75, spec 0.93, Kappa 0.679=substantial agreement). Receiver operator curves for the three most predictive variables and DRI are shown in FIG. 15.

TABLE 6

	NO Dysphagia Sx Before or After Surgery	Dysphagia Sx Before and After Surgery	Dysphagia Sx After Surgery Only	Anova p
Before Surgery				
Distal TNadImp- PeakP sec	40 ± 0.3	2.7 ± 0.4	2.2* ± 0.4	0.043
Distal IBP Slope mmHg/sec	2 ± 1	7 ± 2	10 ± 3	0.089
IBP mmHg	10 ± 2	19 ± 3	18 ± 4	0.133
Dysphagia Risk Index	9 [-2, 19]	40 [16, 97]	61* [22, 508]	0.036
After Surgery				
Distal TNadImp- PeakP sec	3.2 ± 0.7	2.0 ± 0.4	2.2 ± 0.6	0.346
Distal IBP Slope mmHg/sec	8 ± 2	12 ± 3	8 ± 3	0.613
IBP mmHg	10 [8, 13]	18 [14, 22]	14 [3, 29]	0.129
Dysphagia Risk Index	34 ± 14	370 ± 202	-119 ± 272	0.267

Pressure flow variables and the dysphagia risk index for viscous swallows before and after surgery grouped by patients with no dysphagia, dysphagia pre and post-surgery and dysphagia post-surgery only.

P-values are for Kruskal-Wallis One Way Analysis of Variance on Ranks or One Way Analysis of Variance.

*pairwise p < 0.05 vs. No Dysphagia using Multiple Comparison Procedures (Dunn's Method or Holm-Sidak method). Significant comparisons highlighted as black cells.

Example 5

Identification of Pressure-Flow Variables as Markers of Obstruction Along the Pharyngo-Esophageal Segment

[0291] The aim of this experiment was to determine if pressure-flow variables identified by the methods of the present invention could be used to identify the position of an obstruction in the pharynx and/or esophagus of a subject, wherein the obstruction arises as a result of surgery or therapy.

[0292] Obstruction of the UES or esophageal body is a common cause of dysphagia. UES obstruction can occur following radio-therapy for head and neck cancer, following cervical surgery, in relation to neurological diseases such as cerebral palsy and in relation to anatomical abnormalities (bars/strictures). Esophageal body obstruction can occur in relation to formation of strictures/webs which occlude the lumen.

[0293] Regardless of the cause, the ability to identify the precise location of an obstruction may help guide interventions for obstruction (e.g. dilatation). In the pharynx, radiological imaging sometimes is unable to distinguish failure of UES opening due to obstruction vs. failed UES opening to poor bolus propulsion.

[0294] The novel pressure and impedance methods described herein can be applied along the length of the lumen in order identify the precise location of abnormality/inefficiency. By way of example we present two cases of patients with obstruction and how pressure-flow variables, such as the value of NadImp and the TNadImp-PeakP, are altered in the region of the obstruction allowing the position of the obstruction to be identified without the need for radiology.

[0295] Subject 1

[0296] A 58 year old man who developed symptoms post anterior cervical fusion (C5-C6) surgery in whom fluoroscopy demonstrated high obstruction. FIG. 16 shows a radiological image of subject 1 taken during swallowing that identifies a region of narrowing which is adjacent to the metal supports that have been implanted in the cervical spine of the subject. FIG. 17 shows the analysis of pressure and impedance measurements taken from the subject during swallowing.

[0297] Subject 2

[0298] A 13 year old Girl with GERD who received a Nissen Fundoplication operation as a toddler and who has ongoing symptoms of esophageal dysphagia refractory to dilatation of the esophago-gastric junction. Manometry revealed a peristaltic dysfunction with impaired deglutitive EGJ relaxation. When the recorded swallows in this patient are analyzed in a similar fashion to subject 1 (see FIG. 18), a region of obstruction 3-4 cm proximal to the EGJ is identified. Radiologically this region appears as a small esophageal stricture which, whilst observed, was not considered problematic by the attending physician. In contrast the recording identifies this region as being important and therefore a target for intervention in order to achieve symptomatic relief

[0299] Discussion

[0300] The studies performed in subjects 1 and 2 establish the value of measurement of pressure-flow variables along the length of the pharyngo-esophageal segment to identify the precise location of abnormality. We demonstrate two variables which we believe have utility for detecting obstruction; however, it is likely that other pressure-flow variables (as described in previous sections of this specification) may also have utility in this regard. This study also establishes the value of combining different pressure-flow variables to return a more precise indication of the location of the abnormality. Again it is likely that other pressure-flow variables (as described in previous sections of this specification) may also have utility in this regard.

Example 6

Assessment of Esophageal Motor Function with Respect to the Pressure-Flow Variables Zn and ZPp, and Analysis of their Utility as Markers of Obstruction

[0301] In an evaluation of further pressure-flow variables useful for assessing swallowing motor function, the inventor hypothesised that particular impedance measurements could be used to derive diagnostically meaningful information on oesophageal function through a comparison of the impedance signals measured during bolus flow prior to the oesophageal contractile wave with impedance signals measured during the oesophageal contractile wave. Specifically this method relies upon the nadir of impedance preceding the pressure peak (Zn) and the impedance at the time of pressure peak (ZPp).

[0302] During a normal effective swallow, ZPp exceeds Zn by several fold as shown in FIG. 19A. An ineffective swallow is defined when a bolus fails to clear the esophageal lumen. When this occurs, the impedance signal remains low because bolus residue acts as a conductor for current flow between luminal electrodes. During an ineffective swallow, ZPp approaches Zn as shown in FIG. 19B. A further iteration of this concept is one where the oesophageal lumen is physically obstructed, either due to a zone of narrowing, or due to reduced luminal compliance which reduces the degree to

which the lumen can distend/stretch to accommodate passage of a bolus. When this occurs, the reduced cross-sectional area increases the value of Zn such that ZPp drops to below Zn. This is due to the presence of residue and the fact that the oesophageal contractile wave 'bares down' upon the impedance segment with much greater force than normal. Hence a $Zn/ZPp > 1$ is a marker of obstruction over ineffective swallow as shown in FIG. 19C.

[0303] The inventor hypothesised that the value of Zn and ZPp and the relationship of Zn/ZPp may be simple markers of oesophageal function/dysfunction. These variables are easily derived by automated analysis and axial location of the maximum Zn, minimum ZPp and maximum Zn/ZPp may identify the position of an abnormality. This concept is shown in FIGS. 20A-20C where impedance and pressure measurements taken from varying positions distal to the esophago-gastric junction (positions 1-5) are shown. In a normal swallow (FIG. 20A), Zn and ZPp measurements are expected to be consistent at each position such that the Zn/ZPp ratio remains below 1. In an individual with an ineffective swallow that is not due to an obstruction (FIG. 20B), the Zn value at the position of the ineffective swallow (position 3) is expected to increase in comparison to positions 1, 2, 4 and 5 where swallowing motor function is normal. Similarly, the ZPp value at position 3 is expected to approach the Zn value (i.e. decrease) in comparison to positions 1, 2, 4 and 5. As a result, the Zn/ZPp ratio approaches 1. In an individual whose ineffective swallow is due to an obstruction (FIG. 20C), the ZPp value at the position of the obstruction (position 3) is expected to fall below the Zn value at that position. As a result, the Zn/ZPp ratio at the position of the obstruction is greater than 1. This hypothesis was confirmed in the following study.

[0304] Methods

[0305] Fifteen healthy adults (5 M, mean age 33 yrs (20-48) and 15 non-obstructive dysphagia patients were investigated with a combined impedance perfusion manometry catheter incorporating 7 impedance segments (2 cm spaced) and 22 side hole sensors (sensors adjacent impedance array at 2 cm). The catheter was placed with the most distal impedance segment 2 cm proximal to the EGJ junction. Subjects swallowed 5x2 cm and 5x4 cm solid boluses.

[0306] Using commercially available software (Medical Measurement Systems Inc) pressure-impedance recordings were analyzed for standard measures; there were total bolus transit time (TBTT), mean bolus presence time (BPT), distal contractile integral (DCI), size of the 30 mmHg iso contour defect (cm<30ICP). Exported text files of swallows (30 sec at 20 Hz) were also analyzed using our new methods (as per Example 4). Impedance data were standardised to the median for each channel (presented as median standardised units, msu) and analyzed objectively using a MATLAB-based algorithms. The new approach to analysis of pressure-impedance recordings was used to derive pressure-flow variables as detailed in Example 4 (i.e. PNadImp, PeakP, mIBP and TNadImp-PeakP). In addition, changes in the nadir impedance preceding peak pressure (Zn), impedance at the time of peak pressure (ZPp), and the obstructive index (Zn/ZPp), were recorded in association with bolus flow along the oesophageal body (see FIG. 21).

[0307] Results

[0308] 150 control and 150 patient solid bolus swallows were analyzed. Results are shown in Table 7. Of standard pressure-impedance measures, only the 30 mmHg iso-contour defect was altered in patients compared to controls

TABLE 7

	CONTROL	PATIENT
Standard Pressure only and Impedance only Variables		
TBTT	10.1	14.1
Sec	[9.6, 12.4]	[9.6, 12.4]
Mean BPT	7.7	10.3
Sec	[4.7, 10.1]	[8.5, 11.2]
DCI	1465	1279
mmHg	[1206, 2016]	[648, 2441]
cm <30ICP	0.8	3.4*
	[0, 2.1]	[1.2, 4.4]
Pressure-Impedance Pressure-Flow Variables		
Mean Peak P mmHg	46	83*
	[42, 71]	[57, 91]
PNadImp	9	8
	[7, 12]	[6, 11]
Mean IBP mmHg	13	14
	[11, 15]	[6, 18]
Mean TNadImp-PeakP sec	2.6	2.6
	[2.3, 2.7]	[2.4, 3.1]
Pressure Guided Impedance Variables		
Mean Log Zn	-1.9	-0.9***
	[-2.6, -1.4]	[-1.2, -0.8]
Max Log Zn	-4.8	-1.3***
	[-5.2, -4.0]	[-2.7, 0.7]
Min Log ZPp	-0.6	-1.5**
	[-1.2, -0.5]	[-1.7, -1.2]
Max Log Zn/ZPp	-5.1	-0.8***
	[-5.4, -3.7]	[-1.8, 0.2]

Data expressed as median (IQR).

*Mann-Whitney Rank Sum Test

*p < 0.050,

**p < 0.005,

***p < 0.001

[0309] Of pressure-flow variables peak pressure was significantly lower in patients compared to controls (Table 7). In contrast, all impedance only variables based were significantly altered in patients compared to controls, also with great statistical confidence. The data for value and axial position of max Zn, min ZPp and max Zn/ZPp along the esophagus for each individual studied are shown in FIG. 22. There was complete separation of controls and patients based on the value of max Zn, however this variable alone did not differentiate the patients based on the position of the abnormality (FIG. 22A). In contrast, min ZPp was significantly lower in value in patients and the position of the min ZPp was localised significantly more proximally (higher in the esophagus) (FIG. 22B) as was the position of Zn/ZPp (FIG. 22C).

[0310] Conclusions

[0311] These data show that patients with non-obstructive dysphagia can also be differentiated from controls using pressure-guided impedance variables (Zn, ZPp). Whilst it has been demonstrated that standard pressure only variables, impedance only variables and pressure-impedance pressure-flow variables are altered, and can be used to assess swallowing motor function, the greater statistical confidence of differences in Zn and ZPp suggests that these variables are ideal predictors of pharyngeal and/or esophageal dysfunction. In addition, ZPp appears to be a marker of the location of dysfunction. Hence the ratio of Zn/ZPp provides a reliable index of both the degree of pharyngeal and/or esophageal dysfunction as well as the location of the dysfunction. We predict that a Zn/ZPp of >1 is a marker of physical obstruction, and this may allow for targeted intervention to the location of the dysfunction. Alternatively, circumstances of dysphagia

symptoms without an abnormal Zn/ZPp would suggest that the problem may be localised elsewhere, function obstruction of the esophago-gastric junction, to give one example.

Example 7

Apparatus and Software for Enabling an Assessment of Swallowing Motor Function in a Subject

[0312] The methods of the present invention, as described above, can be performed in any manner of means as would be understood by a person skilled in the art. For example, with reference to FIG. 23 there is shown an example apparatus 100 for enabling an assessment of swallowing motor function in a subject according to a sixth aspect of the invention.

[0313] The apparatus 100 communicates with or includes one or more sensors 105, 105a which measure intraluminal impedance and pressure changes, respectively, in the pharynx and/or esophagus of a subject (not shown) during clearance of a bolus from the mouth and/or throat of the subject. In addition and/or as an alternative to the one or more sensors 105, 105a, a server 135 containing intraluminal impedance measurements and pressure measurements previously taken from a subject may be provided, said server 135 being in communication with the apparatus 100.

[0314] The apparatus 100 may for example include a computer 110 which is in communication with the one or more sensors 105, 105a, and/or with the server 135. The computer 110 receives and processes measurements obtained by the one or more sensors 105, 105a or from intraluminal impedance and pressure measurements previously taken from the subject and stored on the server 135. The computer 110 includes a processor 115 for processing and computing various signals received from the one or more sensors 105, 105a, or from previously obtained measurements stored on the server 135, and software to carry out these functions. The software will be described further with reference to FIG. 24.

[0315] The computer 110 may also include a memory 120 for storing data temporarily and running software. A database 125 may be included to store measurements obtained by the one or more sensors 105, 105a. The computer 110 may also include a display 130 for displaying data processed by the processor 115.

[0316] It will be appreciated that the computer 110 may be any one or more of a desktop computer, portable computer, tablet or mobile communication device. The server 135 may be directly connected to the computer 110 or may be connected over a local area network or a network such as the Internet so that the server 135 may be at a remote location. The computer 110 can retrieve intraluminal impedance and pressure measurements previously obtained, as required, and store the measurements on the database 125 or on the server 135, as required.

[0317] The one or more sensors 105 measure intraluminal impedance and this may be measured in any suitable way, as would be understood by a person skilled in the art, and as previously described in detail above. For example, the one or more sensors 105 may be electrodes which are longitudinally spaced on a narrow indwelling catheter, as described above. When placed in the pharynx and/or esophagus of a subject, the electrodes are in electrical contact with the luminal mucosa. A high frequency electrical current is applied through consecutively connected impedance electrode pairs. The spaces between electrodes form linear segments along the catheter. The impedance to current flow for each segment

is measured and stored in the memory 120 or on the database 125 in a sequential scan cycle fast enough to capture the impedance change along the catheter during a swallow accurately.

[0318] Preferably, impedance measurements obtained by the one or more sensors 105 are captured electronically and recorded by the apparatus 100. Impedance patterns may be analyzed by the processor 115 through the visual detection of the occurrence of impedance drops.

[0319] The one or more sensors 105a measure intraluminal pressure changes and these may be measured in any suitable way, as would be understood by a person skilled in the art, and as previously described in detail above. For example, the one or more sensors 105a may form part of an indwelling catheter with pressure changes due to bolus passage being measured and stored in the memory 120 or on the database 125 of the computer 110.

[0320] In some embodiments, both pressure and impedance measurements can be obtained simultaneously by providing a single catheter which incorporates the impedance electrodes and pressure sensors.

[0321] In the operation of one embodiment, the one or more sensors 105, 105a communicate with the computer 110, which receives the impedance and pressure information from the one or more sensors 105, 105a, and combines and analyzes this information via encoded instructions to derive a value for one or more pressure flow variables in order to assess swallowing motor function in the subject. Details with respect to analysis of combined impedance and pressure measurements and derivation of a value for one or more pressure flow variables is described in detail above. It will be clearly understood that in an alternative embodiment, impedance and pressure measurements that have previously been obtained from a subject may be received by the computer 110 from data which has been stored either on the database 125 or obtained via the server 135. Analysis of the data stored on the database 125, obtained via the server 135, or obtained directly from the sensors 105, 105a may be carried out in hardware (such as on a processor 115) or software running in the memory 120.

[0322] FIG. 24 describes a method 200 for assessing swallowing motor function in a subject according to a first aspect of the present invention. In this embodiment, the method 200 is carried out by the computer 110 or on software running in the memory 120. At step 205 intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject are accessed or received. As indicated above, this may be done in real-time from a subject via the one or more sensors 105, 105a and a computer 110, as also discussed with reference to FIG. 23. Alternatively, data can be accessed or received from the database 125 or the server 135 which contains impedance and pressure measurements that have previously been obtained from a subject. Control then moves to step 210 where the intraluminal impedance and pressure measurements are combined and analyzed to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject. This step may be carried out by the processor 115 on the computer 110. Control then moves to step 215 where swallowing motor function in the subject is assessed by performing a comparison between the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables. The comparison may be carried out by the proces-

sor 115 on the computer 110. The predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables may be stored in the database 125, on the server 135, and/or in the memory 120 of the computer 110. Finally, at step 220 an assessment of swallowing motor function in the subject on the basis of the comparison is provided as an output. The assessment is preferably displayed on the display 130 of the computer 110 and/or stored on the database 125 or the server 135.

[0323] The method 200 may further include the step of providing an alert via display 130 if ineffective swallowing in the subject on the basis of the comparison is identified. In addition, the method 200 may further include the step of determining and outputting via the display 130 the risk of aspiration in the subject, a diagnosis of an increased likelihood of aspiration in the subject, a prediction of aspiration in the subject, and/or identifying that the subject is susceptible to aspiration. Alternatively, or in addition, the method 200 may include the step of determining and outputting via the display 130 a prediction for the occurrence of dysphagia in the subject following therapy and/or surgery. Alternatively, or in addition, the method 200 may include the step of generating a swallow risk index, a dysphagia risk index and/or an obstructive risk index. Alternatively, or in addition, the method 200 may include the step of determining the location of an obstruction which is causing ineffective swallowing.

[0324] FIG. 25 describes a method 300 for assessing swallowing motor function in a subject according to a second aspect of the present invention. In this embodiment, the method 300 is carried out by the computer 110 or on software running in the memory 120. At step 305 intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject are accessed or received. As indicated above, this may be done in real-time from a subject via the one or more sensors 105, 105a and a computer 110, as also discussed with reference to FIG. 23. Alternatively, data can be accessed or received from the database 125 or the server 135 which contains impedance and pressure measurements that have previously been obtained from a subject. Control then moves to step 310 where the intraluminal impedance and pressure measurements are combined. This step may be carried out by the processor 115 on the computer 110. Control then moves to step 315 where a swallow risk index for the subject is generated based on a combination of a value of more than one pressure-flow variable in the pharynx and/or esophagus of the subject, wherein the value is derived from an analysis of the combined intraluminal impedance and pressure measurements. This step may be carried out by the processor 115 on the computer 110. Control then moves to step 320 where swallowing motor function in the subject is assessed by performing a comparison between the swallow risk index for the subject to a predetermined reference swallow index. The comparison may be carried out by the processor 115 on the computer 110. The predetermined reference swallow index may be stored in the database 125, on the server 135, and/or in the memory 120 of the computer 110. Finally, at step 325 an assessment of swallowing motor function in the subject on the basis of the comparison is provided as an output. The assessment is preferably displayed on the display 130 of the computer 110 and/or stored on the database 125 or the server 135.

[0325] The method 300 may further include the step of providing an alert via display 130 if ineffective swallowing in

the subject on the basis of the comparison is identified. In addition, the method 300 may further include the step of determining and outputting via the display 130 the risk of aspiration in the subject, a diagnosis of an increased likelihood of aspiration in the subject, a prediction of aspiration in the subject, and/or identifying that the subject is susceptible to aspiration. Alternatively, or in addition, the method 200 may include the step of determining and outputting via the display 130 a prediction for the occurrence of dysphagia in the subject following therapy and/or surgery. Alternatively, or in addition, the method 200 may include the step of generating a dysphagia risk index.

[0326] FIG. 26 describes a method 400 for assessing swallowing motor function in a subject according to a third aspect of the present invention. In this embodiment, the method 400 is carried out by the computer 110 or on software running in the memory 120. At step 405 intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject are accessed or received. As indicated above, this may be done in real-time from a subject via the one or more sensors 105, 105a and a computer 110, as also discussed with reference to FIG. 23. Alternatively, data can be accessed or received from the database 125 or the server 135 which contains impedance and pressure measurements that have previously been obtained from a subject. Control then moves to step 410 where the intraluminal impedance and pressure measurements are combined. This step may be carried out by the processor 115 on the computer 110. Control then moves to step 415 where an obstructive risk index for the subject is generated based on a combination of a value of more than one pressure-flow variable in the pharynx and/or esophagus of the subject, wherein the value is derived from an analysis of the combined intraluminal impedance and pressure measurements. This step may be carried out by the processor 115 on the computer 110. Control then moves to step 420 where swallowing motor function in the subject is assessed by performing a comparison between the obstructive risk index for the subject to a predetermined reference obstructive index. The comparison may be carried out by the processor 115 on the computer 110. The predetermined reference obstructive index may be stored in the database 125, on the server 135, and/or in the memory 120 of the computer 110. Finally, at step 425 an assessment of swallowing motor function in the subject on the basis of the comparison is provided as an output. The assessment is preferably displayed on the display 130 of the computer 110 and/or stored on the database 125 or the server 135. The method 400 may further include the step of providing an alert via display 130 if ineffective swallowing in the subject on the basis of the comparison is identified.

[0327] The pressure flow variables, tools, methods, and apparatus described above have been described and explained primarily in relation to the upper gastro-intestinal tract, including the pharynx and esophagus. However, those pressure flow variables, tools, methods, and apparatus are also applicable and can be used and adapted for use in other parts of the gastro-intestinal tract, including the lower gastro-intestinal tract (for example, duodenum, small intestine, large intestine, anus, etc.), as will be understood by persons skilled in the art once they understand the principles of this of the pressure flow variables, tools, methods, and apparatus described above. Of course, those pressure flow variables, tools, methods, and apparatus are also applicable and can be

used and adapted for use in other mammals, for example, large and small animals and marine mammals.

[0328] The foregoing description of the invention has been presented for purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise form disclosed, and other modifications and variations may be possible in light of the above teachings. The embodiment was chosen and described in order to best explain the principles of the invention and its practical application to thereby enable others skilled in the art to best utilize the invention in various embodiments and various modifications as are suited to the particular use contemplated. It is intended that the appended claims be construed to include other alternative embodiments of the invention except insofar as limited by the prior art. The words “comprise,” “comprises,” “comprising,” “include,” “including,” and “includes” when used in this specification are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

1. A method for assessing swallowing motor function in a subject, the method including:

- (a) accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;
- (b) combining and analysing the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject, including at least one of the pressure flow variables a group consisting of iZn/Z, IBP max, and FSP; and
- (c) assessing swallowing motor function in the subject by comparing the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.

2. An apparatus for enabling an assessment of swallowing motor function in a subject, the apparatus including:

- (a) a processor;
- (b) a memory; and
- (c) software resident in memory accessible to the processor, the software executable by the processor to carry out a method comprising:

accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;

- (b) combining and analysing the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject, including at least one of the pressure flow variables a group consisting of iZn/Z, IBP max, and FSP; and
- (c) assessing swallowing motor function in the subject by comparing the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.

3. A computer readable media including a set of instructions in the form of a computer software program, the instructions

being executable by a processing device on-board a programmed computer, wherein execution of the instructions causes the programmed computer to:

- (a) accept, as an input, intraluminal impedance and pressure measurements obtained from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject;
- (b) combine and analyze the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject, wherein the pressure flow variables include, but are not limited to, at least one of the pressure flow variables in a group consisting of iZn/Z, IBP max, and FSP;
- (c) assess swallowing motor function in the subject by performing a comparison between the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables; and
- (d) provide, as an output, an assessment of swallowing motor function in the subject on the basis of the comparison.

4. The computer readable media according to claim 3, wherein the computer readable media further includes executable instructions which identify ineffective swallowing in the subject on the basis of the comparison.

5. The computer readable media according to claim 3, wherein the computer readable media further includes executable instructions which determine risk of aspiration in the subject, diagnose an increased likelihood of aspiration in the subject, predict aspiration in the subject, and/or identify a subject susceptible to aspiration.

6. The computer readable media according to any one of claim 5, wherein the computer readable media further includes executable instructions which predict the occurrence of dysphagia in the subject following therapy and/or surgery.

6. A combination product, the combination product including:

- (a) a device for obtaining intraluminal impedance and pressure measurements from the pharynx and/or esophagus of a subject during clearance of a bolus from the mouth and/or throat of the subject; and
- (b) software executable by the device for performing a method comprising:
 - (i) accessing intraluminal impedance measurements and pressure measurements obtained from the pharynx and/or esophagus of the subject during clearance of a bolus from the mouth and/or throat of the subject;
 - (ii) combining and analysing the intraluminal impedance and pressure measurements to derive a value for one or more pressure-flow variables in the pharynx and/or esophagus of the subject, including at least one of the pressure flow variables a group consisting of iZn/Z, IBP max, and FSP; and
 - (iii) assessing swallowing motor function in the subject by comparing the value of the one or more pressure-flow variables with a predetermined pharyngeal and/or esophageal reference value for the one or more pressure-flow variables.

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专利名称(译)	吞咽运动功能测量和评估工具，方法和装置		
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摘要(译)

提供了工具，方法和装置，其可用于识别受试者中的无效吞咽，包括由于阻塞引起的无效吞咽，并且还可用于确定受试者中的抽吸风险。在一个方面，一种方法包括在从受试者的口腔和/或咽喉清除推注期间访问从受试者的咽和/或食道获得的腔内阻抗测量值和压力测量值。该方法还包括组合和分析管腔内阻抗和压力测量结果，以得出受试者的咽和/或食道中的一个或多个压力 - 流量变量的值。通过将压力 - 流量变量的值与一个或多个压力 - 流量变量的预定咽和/或食道参考值进行比较来评估受试者中的吞咽运动功能。

